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CLINICAL RESEARCH

Incidence of gallstone disease in Italy: Results from a multicenter, population-based Italian study (the MICOL project)

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Abstract

AIM: To evaluate gallstone incidence and risk factors in a large population-based study.

METHODS: Gallstone incidence and risk factors, were evaluated by structured questionnaire and physical examination, respectively, in 9611 of 11 109 (86.5%) subjects who were gallstone-free at the cross-sectional study.

RESULTS: Six centers throughout Italy enrolled 9611 subjects (5477 males, 4134 females, aged 30-79 years), 9517 of whom were included into analysis: 424 subjects (4.4%) had gallstones and 61 (0.6%) had been cholecystectomized yielding a cumulative incidence of 0.67% per year (0.66% in males, 0.81% in females). Increasing age, a high body mass index (BMI), a history of diabetes, peptic ulcer and angina, and low cholesterol and high triglyceride levels were identified as risk factors in men while, in females, the only risk factors were increasing age and a high BMI. Increasing age and pain in the right hypochondrium in men and increasing age in females were identified as predictors of gallstones. Pain in the epigastrium/right hypochondrium was the only symptom related to gallstones; furthermore, some characteristics of pain (forcing to rest, not relieved by bowel movements) were significantly associated with gallstones. No correlation was found between gallstone characteristics and clinical manifestations, while increasing age in men and increasing age and BMI in females were predictors of pain.

CONCLUSION: Increasing age and BMI represent true risk factors for gallstone disease (GD); pain in the right hypochondrium and/or epigastrium is confirmed as the only symptom related to gallstones.

Key words: Gallstone disease; Ultrasonography; Epidemiology; Prevalence; Incidence; Abdominal pain; Cholecystectomy; Body mass index

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INTRODUCTION

Gallstone disease (GD) is a very common gastrointestinal disorder, presents mainly in the Western world[1,2]. Although this disease has a low mortality rate, its economic and health impact is significant due to its high morbidity. In fact, GD is one of the most common abdominal conditions for which patients in developed countries are admitted to hospitals[3], and this frequency has increased in Western countries since the 1950s[4]. GD is considered "a surgical disease"

since only a cholecystectomy is capable of definitively curing the disease[5]. However, since the introduction of laparoscopic cholecystectomy in the early 90s, which is considered a safe treatment for GD[6], a possible unjustified increase in surgical procedures has been observed[7]. Therefore, there is the need for more knowledge of the epidemiological characteristics of GD in order to better identify therapeutic strategies.

The availability of ultrasonography (US) as an accurate tool for gallstone diagnosis has allowed the evaluation of gallstone prevalence by means of epidemiological surveys of the general population, both in Eastern and Western countries[8,9]. Furthermore, these studies, as well as case-control studies, have allowed the identification of the factors most frequently associated with GD, i.e. increasing age, female sex, familial history of GD, number of pregnancies, obesity, or type 2 diabetes[10].

However, only a few prospective US surveys, mainly in Europe[11-14], have been carried out which aimed measuring the gallstone incidence rate and risk factors for the disease. The knowledge of disease risk factors is crucial to carrying out primary or secondary preventive programs.

The Multicenter Italian Study on Epidemiology of Cholelithiasis (the MICOL project) is a population-based cross-sectional study which began in 1985 and extended since 1998 and it was designed to obtain an overview of the distribution of GD in Italy according to different regions and ages[15]. Results on prevalence distribution, associated factors, and clinical manifestations have been extensively reported in previous articles[15-17].

This article reports the incidence rate and risk factors for GD which were evaluated in six units belonging to the MICOL project.

MATERIALS AND METHODS

Study design

The MICOL project is a population-based, cross-sectional study carried out in 8 Italian regions by different operative units. Complete details on the study protocol have been published elsewhere[15]. The project plan includes 2 cross-sectional surveys; the first began in 1985 and was completed in 1988 and the second survey was carried out on the same subjects 10 years later in order to estimate the incidence of GD as well as its natural history. Seven of the original operative units were able to complete the second survey.

Subjects

After 10 years, all participants in the first survey were invited to a follow-up examination. Preliminarily, using the electoral lists, subjects who had died or moved were identified. The remaining subjects received a standardized invitation for a general health examination and an US examination of the upper abdomen. Subjects who did not respond were invited again; those who refused to participate or those who did not respond at all were contacted by telephone.

Screening protocol

The re-examination took place between 1995 and 1998. Subjects who were found to have had gallstones or a previous cholecystectomy for gallstones at the first survey were studied separately, the major aim of this re-examination being evaluation of the natural history of gallstones.

Similarly to what had been carried out in the first survey[15], the screening protocol included upper abdominal US, physical examination, fasting blood specimen collection, and administration of a precoded questionnaire. This questionnaire inquired about family and personal history, dietary habits, past and current use of medications, and the presence of comorbidities (diabetes, chronic heart disease, liver cirrhosis, peptic ulcer); the questionnaire also included a specific section aimed at assessing the occurrence/presence of abdominal symptoms (details of the structure of the questionnaire as well as details on its items have been published elsewhere[17]). The questionnaire was administered by trained interviewers selected from the medical staff of each operative unit. Upper abdominal US was performed thereafter by independent physicians.

Statistical analysis

The incidence rate for new-onset gallstones was determined from baseline to the second examination, after adjustment for age and gender. Logistic regression analysis was carried out providing risk factors and Odd Ratios (OR) for developing gallstones; Cox proportional hazard regression was used to calculate hazard ratios.

According to previous results regarding associated factors obtained from the gallstone prevalence study[15] and from available literature data[8,10,18], different factors were evaluated by means of logistic regression analysis as possible risk factors for GD including age, gender, educational level, family history of gallstones, body mass index (BMI) (measured both at the prevalence and the incidence studies), number of pregnancies, history of diets, diabetes, peptic ulcer, inflammatory bowel disease, liver cirrhosis, smoking, coffee drinking, and serum levels of total cholesterol, HDL-cholesterol, and triglycerides.

To identify the possible role of the disease status on clinical presentation, patients were subsequently classified into 4 groups according to their disease status: gallstone-free subjects (GF), patients with gallstones not previously diagnosed (GNDP), patients with previously diagnosed gallstones (GPD), and patients with a history of cholecystectomy for gallstones (CC).

Logistic regression models were created for the latter 3 groups, using the gallstone-free subjects as the comparison group.

As a consequence of the results of the logistic regression models, patients referring pain located at the right hypochondrium or epigastrium were selected and further evaluated.

A multivariate analysis was subsequently carried out using logistic regression and, for each gallstone group, a model was created using the gallstone-free subjects

as the comparison group. SPSS (ver.9.0 for windows) statistical software was used. A probability of $P < 0.05$ was considered significant.

RESULTS

Subjects

Out of the 12709 potentially enrolled subjects belonging to the seven participating units, 502 died and 1098 transferred. Among the dead subjects, one case of gallbladder cancer was observed, which translates in a mortality rate for this cause of 2.5/10000 per year.

Of the 11109 enrolled subjects, 9611 (5477 males, 4134 females, aged 30-79 years) were evaluated (86.5%). The attendance rate was different in different age classes, greater in younger than in older subjects (83% in the 40-60 years old group and 74% in the > 60 years old group) while no difference was documented between the sexes (78% in males, 89% in females). The mean follow-up period was 8 years.

On the basis of US diagnosis, 9517 (5428 males, 4089 females) were suitable for analysis since, in 94 cases, the US diagnosis was biliary sludge (35 cases) or gallbladder polyps (40 cases); in 19 cases, the US diagnosis was uncertain. These 94 cases were excluded from the study, since no definitive data are available in literature regarding these aspects as true gallstones[5,10,11].

Four hundred and twenty-four subjects (206 males, 218 females) (4.4%) were found to have gallstones and 61 (26 males, 35 females) (0.6%) had been cholecystectomized for gallstones during the follow-up period.

The cumulative incidence rate of GD thus was 0.67% per year [0.66% per year in males, 0.81% per year in females (Table 1)]. Table 1 also shows the incidence rate among the different operative units.

Table 2 reports the morphological characteristics of gallstones; incident gallstones were more frequently small in size (77.9% less than 1.5 cm); no difference was observed between males and females in terms of gallstone number or size.

According to the disease status evaluation, of the 9517 subjects enrolled in the study, 9032 (94.5%) were GF; 312 (3.3%) were GNPD, 112 (1.2%) were GPD, and 61 (0.6%) were CC.

Table 1 Incidence of GD in the different operative units of the MICOL project

Operative unit	Overall % yr	Male	Female
Bologna Loiano	0.50	0.50	0.50
Bologna Brisighella	0.61	0.60	0.80
Bolzano	0.82	0.50	1.10
Castellana Grotte	0.75	0.70	0.80
Tivoli	0.64	0.50	0.70
Modena San Lazzaro	0.43	0.40	0.40
Modena Madonnina	0.86	0.60	1.20
Overall	0.67	0.66	0.81

Table 2 Characteristics of newly developed gallstones

Characteristics		%	*P*
Overall			
Number	Single	48.90	< 0.0001
	Multiple	51.10	
Size	⩽ 1.5 cm	77.90	< 0.0001
	⩾ 1.5 cm	22.10	
Male			
Number	Single	44.80	< 0.0001
	Multiple	55.20	
Size	⩽ 1.5 cm	78.70	< 0.0001
	⩾ 1.5 cm	21.30	
Female			
Number	Single	52.30	< 0.0001
	Multiple	47.70	
Size	⩽ 1.5 cm	77.10	< 0.0001
	⩾ 1.5 cm	22.90	

Table 3 Risk factors for GD

Factor	Coefficient	SE	*P*
Men			
Age	0.0405	0.0071	< 0.000
BMI	0.0536	0.0195	< 0.006
HDL cholesterol	-0.0118	0.0059	< 0.040
Cholesterol	-0.0034	0.0016	< 0.030
Triglycerides	0.0004	0.0001	< 0.007
Diabetes	0.5293	0.2220	< 0.010
Peptic ulcer	0.4378	0.1753	< 0.010
Women			
Age	0.0279	0.0073	< 0.000
BMI	0.0178	0.0147	< 0.000

Logistic regression analysis: regression coefficients, corresponding SE, and *P* values for single factors and interactions, significantly associated with gallstones.

Risk factors and predictors for GD

Risk factors for GD: The results of the logistic regression analysis carried out to identify the risk factors for GD are shown in Table 3.

Among the factors considered, in males, increasing age ($P < 0.0001$), a high BMI ($P < 0.006$), a history of diabetes ($P < 0.01$) and of peptic ulcer ($P < 0.01$), low levels of total ($P < 0.03$) and HDL ($P < 0.04$) cholesterol, and high levels of triglycerides ($P < 0.007$) were identified as risk factors.

In females, only increasing age ($P < 0.00001$) and a high BMI ($P < 0.0001$) were identified as risk factors for GD.

When evaluating the risk factor distribution according to the classification of the patient's clinical status (Table 4), no differences were observed in terms of age, BMI, and biochemical parameters while the presence of comorbidities increased among the three groups; in particular in males, diabetes, peptic ulcer, and myocardial infarction while, in females, peptic ulcer and myocardial infarction.

Predictors of GD: The evaluation of predictive factors for the presence of GD (Table 5) in patients with abdominal pain indicated that these were increasing age ($P < 0.04$) and pain in the right hypochondrium ($P < 0.03$) in males with gallstones and only increasing age

Table 4 Risk factors for GD

Factor OR (95% CI)	Gallstones not previously diagnosed (*n* = 312)	Gallstones previously diagnosed (*n* = 112)	Cholecystectomized (*n* = 61)
Men			
Age	1.03 (1.01-1.05)	1.05 (1.02-1.07)	1.01 (0.97-1.06)
BMI	1.06 (1.01-1.11)	1.03 (0.97- 1.10)	1.07 (0.96-1.06)
HDL cholesterol	0.99 (0.97-1.004)	0.98 (0.96-1.00)	1.00 (0.97-1.03)
Cholesterol	0.99 (0.99-1.00)	0.99 (0.98-0.99)	1.00 (0.99-1.01)
Triglycerides	1.00 (0.99-1.00)	1.00 (1.00-1.01)	0.99 (0.99-1.00)
Diabetes	1.75 (1.04-2.96)	1.60 (0.77-3.32)	2.72 (0.89-8.33)
Peptic ulcers	1.11 (0.69-1.77)	2.53 (1.52-4.20)	3.38 (1.48-7.72)
Myocardial infarction	0.99 (0.99-1.00)	1.27 (0.38-4.23)	1.43 (0.18-11.18)
Women			
Age	1.01 (1.00-1.03)	1.04 (1.02-1.07)	0.98 (0.94-1.02)
BMI	1.08 (1.04-1.12)	1.05 (1.00-1.11)	1.07 (0.99-1.15)
HDL cholesterol	1.00 (0.99-1.01)	0.98 (0.97-1.00)	0.98 (0.95-1.00)
Cholesterol	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.01)
Triglycerides	1.00 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Diabetes	1.10 (0.58-2.09)	0.48 (0.14-1.58)	1.00 (0.22-4.49)
Peptic ulcers	0.67 (0.34-1.34)	0.70 (0.28-1.76)	3.55 (1.57-8.04)
Myocardial infarction	1.83 (0.99-1.00)	3.15 (0.70-14.18)	12.82 (2.69-60.94)

OR calculated by logistic regression analysis; regression coefficients, corresponding standard errors, and *P* values for single factors and interactions, significantly associated with gallstones.

Table 5 Predictors of GD in patients with abdominal pain

Variables	Gallstones			Cholecystectomized		
	P	OR	95% CI	*P*	OR	95% CI
Male						
Age	0.04	1.033	1.00-1.06	0.02	1.05	1.00-1.10
Pain in the right hypochondrium	0.03	2.35	1.04-5.3	0.62		
Pain in the epigastrium	0.68	1.19		0.66		
Female						
Age	0.000	1.053	1.02-1.08	0.50		
Pain in the right hypochondrium	0.36			0.01	14.64	1.83-116.81
Pain in the epigastrium	0.09			0.002	24.19	3.18-183.92

Table 6 Predictors of GD according to the presence of concomitant diseases

Variables	Gallstones			Cholecystectomized		
	P	OR	95% CI	*P*	OR	95% CI
Male						
Age	0.0000	1.03	1.02-1.05	0.385		
Diabetes	0.0008	2.09	1.36-3.22	0.055		
Peptic ulce	0.04	1.44	1.01-2.05	0.004	3.28	1.45-7.41
Cirrhosis	0.002	1.79	1.08-2.97	0.000	5.73	2.13-15.42
Female						
Age	0.0000	1.03	1.01-1.04	0.409		
Diabetes	0.522			0.208		
Peptic ulcer	0.186			0.004	3.19	1.43-7.08
Cirrhosis	0.388			0.742		

($P < 0.0001$) in females with gallstones; in cholecystectomized male patients, the only factor was increasing age ($P < 0.02$) while, in cholecystectomized females, pain in the right hypochondrium ($P < 0.01$) and the epigastrium ($P < 0.002$) were the predictive factors.

Considering only the effect of comorbidities, the evaluation of predictive factors for the presence of GD indicated that, in males with gallstones, these factors were increasing age ($P < 0.0001$), the presence of diabetes ($P < 0.001$), peptic ulcer ($P < 0.04$), and liver cirrhosis ($P < 0.002$) while, in females with gallstones, only increasing age ($P < 0.0001$) (Table 6) was a predictor of GD; in cholecystectomized male patients peptic ulcer ($P < 0.004$) and liver cirrhosis ($P < 0.0001$) were predictors while, in female patients, only peptic ulcer ($P < 0.004$) appeared as a predictor of the disease.

Clinical manifestation of GD

The distributions of abdominal symptoms in the four groups are reported in Table 7. No differences among the groups were documented in terms of frequency for non-specific symptoms, with the exception of nausea, while pain in the epigastrium and the right hypochondrium were related to GD and varied according to the disease categories.

In Table 8, the characteristics of abdominal pain in the considered groups are reported: some characteristics resulted significantly associated with GD, showing a progressive increase in the ORs throughout the disease categories; pain necessitating rest, pain not relieved by bowel movements and the presence of clinical signs of gallstone complications (jaundice, fever, dark urine).

Predictive factors for biliary pain

No correlation was found between US gallstone characteristics (number and size) and their presence or clinical manifestation.

In males with GD, increasing age was the only predictor of biliary pain (mainly pain in the right hypochondrium) while, in females, BMI was also related to pain (mainly pain in the epigastrium). No correlation was found between comorbidities and GD.

Table 7 Distribution of symptoms (and unadjusted ORs) in gallstone-free subjects, patients with gallstones not previously diagnosed, patients with a previous diagnosis of gallstones, and patients with a history of cholecystectomy for gallstones

Symptoms (%) OR (95% CI)	Gallstone-free subjects (n = 9001)	Gallstones not previously diagnosed (n = 312)	Gallstones previously diagnosed (n = 112)	Cholecystectomized (n = 61)
Belching	19.1	19.5	27.2	23.1
		1.03 (0.75-1.39)	1.27 (0.86-1.89)	0.92 (0.48-1.75)
Heartburn	32.2	33.1	37.5	44.2
		1.12 (0.85-1.39)	0.89 (0.61-1.30)	1.29 (0.72-2.03)
Nausea	12.3	14.3	18.4	26.9
		1.22 (0.82-1.82)	1.48 (0.90-2.42)	2.40 (1.19-4.83)
Vomiting	7.2	7.7	9.6	9.6
		0.99 (0.59-1.64)	0.79 (0.41-1.53)	0.97 (0.40-2.33)
Bloated feeling after meals	37.2	38.6	44.9	48.1
		1.24 (0.95-1.61)	1.12 (0.78-1.63)	1.24 (0.69-2.21)
Epigastric discomfort	33.8	33.1	40.4	38.5
		0.96 (0.72-1.26)	1.26 (0.87-1.83)	0.87 (0.48-1.59)
Bitter taste in the morning	36.4	35.4	41.2	44.2
		0.93 (0.71-1.21)	0.88 (0.61-1.26)	1.08 (0.61-1.88)
Heavy feeling on the right side	19.7	18.8	25.7	28.8
		0.94 (0.68-1.29)	1.14 (0.77-1.71)	1.09 (0.58-2.05)
Heavy feeling in the epigastrium	22.7	21.3	25.0	26.9
		0.83 (0.60-1.15)	0.81 (0.53-1.24)	0.67 (0.34-1.33)
Pain in the epigastrium	11.2	24.7	39.0	51.2
		1.5 (1.17-2.4)	3.0 (2.6-5.7)	29.9 (7.0-221.3)
Pain in the right hipocondrium	15.8	23.7	39.0	46.5
		1.7 (1.3-2.8)	3.9 (3.1-7.4)	32.1 (9.3-238.9)
Intolerance to fatty or fried foods	24.0	5	4.4	3.4
		0.99 (0.63-1.55)	0.94 (0.19-1.79)	1.04 (0.5-2.14)

DISCUSSION

The present study evaluated incidence and risk factors for GD in a large population from various Italian regions, thus providing a more detailed picture of the epidemiological characteristics of this disease. Incidence was higher in females than in males and increased with age. In our population, the risk factors for GD in males were increasing age, BMI, concomitant diseases such as diabetes, liver cirrhosis, peptic ulcer, coronary disease, HDL and total cholesterol, and high levels of triglycerides while, in females, only increasing age and BMI. Increasing age, pain in the right hypochondrium/epigastrium, and the presence of concomitant diseases are predictors of GD. Pain in the right hypochondrium or epigastrium was the only symptom associated with GD; symptom severity increased as a function of the natural history of the disease. Increasing age in men and aging and BMI in females were the only predictive factors for the eventual presence of symptoms.

GD is a very common gastrointestinal disorder mainly in the Western world[1,2]; although this disease has a low mortality rate, its economic and health impact is significant due to its high morbidity. In fact, GD is one of the most common abdominal conditions for which patients are admitted to hospitals in developed countries[3]. Knowledge of disease epidemiology is therefore crucial in managing this disorder, not only for planning preventive programs, but also for the identification of the best therapeutic strategy. Several US-based surveys have been carried out in Europe[19-23] and in North[24,25] and South[26] America as well as in Asia[27,28], indicating prevalence rates for GD ranging from 5.9%[20] to 21.9%[22]. However, few studies[11-14] have been carried out to evaluate incidence and risk factors of GD, mainly due to the difficulties in following up large populations for several years. The MICOL study was designed to obtain a general overview of GD in Italy, investigating GD in terms of prevalence, incidence, risk factors, and natural history[15]. In the present study, a large general population was evaluated with the objective of identifying gallstone incidence and risk factors as well as the morphological and clinical characteristics of newly developed gallstones. Incidence was higher than that measured in previous Italian studies[12-14]; these differences could be related to the small population sample evaluated in the earlier studies. Furthermore, prevalence was also higher than in Denmark (4.5% and 5.8%, in males and females, respectively)[11]. Differences in research design may justify these differences even it is not possible to exclude the role of environmental factors.

In the present study, the response rate was higher (79%) than that reported in other GD incidence surveys performed in the north (63.7)[12] and in the centre (73.5%)[14] of Italy and similar to that observed in Denmark (82.8%)[11] and in southern Italy (87.7%)[13]; this percentage indicates a high adherence of the target population to the epidemiological study.

The participation rate was also higher in the present incidence study (79%) than in the previous study evaluating GD prevalence (64.4%)[15]; this difference could be related to a possible self-selection of patients or to an effect of dilution in the prevalence study since, in that study, 14 units participated while, in the present study, only 7 units were able to adhere to the protocol.

Table 8 Distribution of pain characteristics (and unadjusted ORs) in subjects reporting abdominal pain

Characteristics of Pain	Gallstone-free subjects	Gallstones not previously diagnosed (*n* = 312)	Gallstones previously diagnosed (*n* = 112)	Cholecystectomized (*n* = 61)
Radiation				
Not radiated (%)	53.0	55.4	43.9	53.5
Radiated (%)	37.4	41.5	45.6	46.5
OR (95% CI)		0.97 (0.63-1.50)	1.11 (0.74-1.66)	0.94 (0.57-1.53)
Duration[1]				
< ½ h (%)	30.3	35.5	7.8	16.3
½-1 h (%)	21.1	19.4	21.6	16.3
1-3 h (%)	16.0	19.4	31.4	18.6
> 3 h (%)	32.6	25.8	39.2	48.8
OR (95% CI)		0.89 (0.71-1.10)	1.35 (1.05-1.75)	1.27 (0.96-1.69)
Tollerability				
Not forced to rest (%)	80.5	68.3	62.0	25.6
Forced to rest (%)	19.5	31.7	38.0	74.4
OR (95% CI)		1.98 (1.11-3.51)	2.26 (1.22-4.18)	9.88 (4.82-20.27)
Relationship with meals				
Yes (%)	13.2	9.7	10.2	9.5
No (%)	86.8	90.3	89.8	90.5
OR (95% CI)		1.84 (0.64-5.23)	1.30 (0.47-3.63)	1.29 (0.37-4.47)
During meals				
Yes (%)	2.6	1.7	6.1	
No (%)	97.4	98.3	93.9	100
OR (95% CI)		0.94 (0.12-7.32)	0.38 (0.10-1.48)	129.09 (0.90-4.62)
Soon after meals				
Yes (%)	32.3	24.6	43.1	40.5
No (%)	67.7	75.4	56.9	59.5
OR (95% CI)		1.61 (0.84-3.09)	0.70 (0.37-1.31)	0.63 (0.31-1.25)
After heavy meals				
Yes (%)	24.5	23.8	26.0	23.8
No (%)	75.5	76.2	74.0	76.2
OR (95% CI)		1.02 (0.55-1.91)	0.73 (0.38-1.38)	1.82 (0.77-4.33)
Relieved by bowel movements				
Yes (%)	41	30	28	12.2
No (%)	59	70	72	87.8
OR (95% CI)		2.02 (1.07-3.82)	1.76 (0.99-3.10)	5.35 (2.07-13.76)
Clinical signs of gallstone complications				
Yes (%)	29.9	36.4	47.7	69.4
No (%)	70.1	63.6	52.3	30.7
OR (95% CI)		1.31 (0.69-2.46)	2.13 (1.16-3.94)	5.28 (2.56-10.9)

[1]The category "< ½ h" has been taken as baseline.

We documented variability between the different units in terms of incidence; this difference could be related to the role of environmental factors (life style, dietary habit, *etc*.) even if we were unable to identify any possible difference between the different operative units.

Gender, increasing age, and BMI were confirmed as true risk factors for GD; in males, low levels of cholesterol, high levels of triglycerides, and the presence of co-morbidities such as diabetes, peptic ulcer, angina, and liver cirrhosis represented additional risk factors. These results further confirm the importance of environmental factors in gallstone development, possibly related to an unhealthy life style. In fact, recent epidemiological studies have suggested that GD may be included in those disorders which characterize the metabolic syndrome[29,30]. In particular, a close relationship between obesity and cardiovascular disease (two of the more characteristic features of the metabolic syndrome) and GD has been identified[31,32].

We did not confirm a family history of gallstones, dieting, the number of pregnancies, and the use of contraceptive pills, which were found to be significantly associated with GD in the prevalence study as risk factors[16]. We are unable to interpret the significance of this result; however, the data available on some risk factors for GD are frequently conflicting[8,10]. The prospective cohort design of the present study and the use of US as the diagnostic tool have reduced the possibility of a recall and other information bias; furthermore, the high response rate makes selection bias unlikely.

An important result of the present study is related to the clinical manifestation of incident gallstones. In fact, we have confirmed the observation made in the prevalence study[15,17] that pain in the right hypochondrium and/or epigastrium is the only symptom significantly associated with gallstones while the so-called "non-specific biliary symptoms", i.e. dyspeptic symptoms, showed the same frequency in gallstone-free subjects and GD patients.

We have also confirmed our previous observation[17] concerning the usefulness of splitting the subjects

enrolled in the study into 4 categories reproducing the different stages of GD (absence of disease, silent disease, overt disease, severe disease); in fact, the frequency and severity of the clinical symptoms and the signs of GD increased throughout the 3 disease categories.

Furthermore, for those characteristics that are an expression of the degree of pain severity (pain forcing to rest, presence of clinical signs of gallstone complications) they progressively increased from silent gallstones to symptomatic gallstones to cholecystectomized patients for gallstones, suggesting that the natural history of GD moves from a silent to a clinically evident stage; this is also true for newly developed gallstones. This information may be useful in choosing the best therapeutic strategy in gallstone patients since surgical treatment is indicated only in true symptomatic gallstone patients[5,33].

Finally, we were unable to identify any predictive factor for the presence of biliary pain in terms of gallstone characteristics (number and size), while increasing age in males and a high BMI in females were related to the presence of biliary pain. These results are in agreement with some[34], but in disagreement with others[35,36].

In conclusion, this study provides data on the gallstone incidence and risk factors for GD in a large free-living population; the incidence rate is higher in females and it increases with age. Increasing age and BMI represent true risk factors for GD; pain in the right hypochondrium and/or epigastrium is confirmed as the only symptom related to GD; pain, as well as its characteristics of disease severity, increases in severity and frequency throughout the different stages of GD (from silent to severe disease). This information may help physicians in clinical decision making.

COMMENTS

Background

Gallstone incidence and risk factors are poorly understood and the relationship between gallstone presence and its clinical manifestations is debated.

Research frontiers

Gallstone incidence, risk factors, and clinical manifestations.

Innovations and breakthroughs

The present paper provides important information on gallstone incidence and risk factors and clearly identifies the clinical manifestations of the disease.

Applications

The results of the present paper can be useful for the early recognition of gallstones and for deciding the most appropriate therapeutic management according to the clinical presentation. Furthermore, preventive strategies can be identified and planned according to these results.

Peer review

This manuscript is a multicenter Italian study giving information about the incidence of gallstone disease in Italy. The results of this study can provide information for the comparison of Italian population results with the other nations' results.

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