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Research Article

Foods and nutrients consumption and the risk of gallstone disease: A nested case-control study in Rosario, Argentina

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Abstract

The etiology of Gallstone Disease (GD) is multivariate and it involves genetics and environmental factors. Nutritional exposure is considered the main environmental influence that contributes to gallstone formation. The aim of this study was to assess the association between diet and GD. A nested case-control study based on a previous representative screening of asymptomatic subjects living in Rosario, Argentina, was carried out. Participants underwent a personal interview. Food and nutrient intake were estimated by applying a food-frequency questionnaire, a food photography atlas, and software for food composition. Logistic regression analysis was used to estimate Odds Ratios (OR) and 95% confidence intervals, adjusted by potential confounders. A total of 120 patients, 51 cases and 69 controls, were studied. Statistically significant differences in average daily energy intake were found between cases and controls (p = 0.002). Total fats, chicken with skin, sausages, and cold cuts intakes were higher in the cases group. However, the control group was characterized by a statistically significant higher consumption of vegetables, fresh fruits, nuts, chicken without skin, and skimmed dairy products. Multiple logistic regression showed that GD risk diminished with red and yellow vegetables (OR = 0.037; p = 0,0004) and nuts consumption (OR = 0.201; p = 0.019). Instead, GD risk increases with total fats (OR = 7.959; p = 0.0205), fatty cattle meat (OR = 18.163; p = 0.0063), and chicken with skin consumption (OR: 10.595; p = 0.0050). Phosphorus consumption decreases GD risk (OR = 0.055; p = 0.0035). A number of meals also acted as a protective factor. Also, caloric intake was a risk factor. Each 100 kilocalories daily consumed; the risk increases by 12%.

Introduction

Gallstones or Gallbladder Stones (GS) are stones in the gallbladder. It is considered that a person suffers from gallstone disease (GD) if gallbladder stones are found, or if there is a history of surgery due to gallstones.

The prevalence of GD varies widely from region to region, and there is a big difference between the East and the West [1]. Using ultrasound as a diagnostic method, it has been found that American and Mexican locals had the highest prevalence rates [1,2], followed by Chilean women offspring of Mapuches. A lower rate was found in Northern European countries, while southern had an even lower prevalence. The lowest prevalence rate was found in Asia, followed by African countries [1,2]. In Uruguay, a study carried out in Montevideo showed a prevalence rate of 10.4% [3]. In Argentina, only two studies were carried out, one by our research group in the city of Rosario and the other in Buenos Aires, showing prevalence rates of 20.5% and 21.9%, respectively [4,5].

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Nutritional exposure is considered the main environmental influence that contributes to gallstone formation.

Westernization of nutrition in modern post–war societies is characterized by a high–calorie diet, low-density nutritional food intake, carbohydrates, and refined fats intake, high energy, low-fiber intake, and low-micronutrient intake. This has led to a chronic hyperalimentation that together with a sedentary lifestyle resulted in an increase in the prevalence of overweight andnoninsulin–dependent diabetes. These nutritional factors have been associated with the potential of producing lithogenic bile. Overweight and obesity are both lithogenic because they increase the cholesterol synthesis and its secretion, which together with a low-fiber intake that is associated with intestinal hypomotility, produced a significantly increased risk of developing a GD [6]. Regarding high–calorie intake, studies about the risk of developing GD are not conclusive, although generally results tend to associate higher calorie intakes with a greater risk. While most studies have suggested a positive association [7-9], a study from Italy showed as the calorie intake increased in men, the risk of GD was reduced, while results in women were not significant [10].

The prevalence of gallbladder stones in vegetarian people is low [11]. In a German national prevalence study conducted on 1116 participants [12], it was found that none of the 48 vegetarians had GD. In addition, fruit and vegetable consumption reacted as a protective factor, both in follow–up studies [13] and incase–control designs [7,14].

In the case–control study carried out in Spain, cases were characterized by a lower intake of fish and fruits, but with a higher intake of grains, oils, and sugar, compared with the corresponding controls. They also consumed more energy and had fewer intakes per day [7]. A study conducted in Greece, also found that cases had lower intakes of vegetables but higher intakes of grains and potatoes, in relation to controls [14].

Nut consumption was associated with a lower risk of cholecystectomy in women who consumed this dried fruit in high quantities, than those who never consumed nuts [15). In men, the risk of developing GD was lower in those who consumed nuts five or more times per week, compared to those who rarely did it [16].

Some recent studies have detected a positive association between total fat intake and the risk of developing the disease [7,8]. Most significant association results, with a higher risk of GD, were found in saturated fats [7,8,17,18]. Regarding monounsaturated fats, the results were not conclusive. Some researchers have associated monounsaturated fats with a higher risk of GD [7], while others have associated a lower risk [17] and others have found no association [8]. It has been hypothesized that cholesterol might be a risk factor for GS. Acase–control study reported a higher intake of cholesterol diet in cases than in controls [7]. In a study from Italy, it was found that cholesterol acts as a protective factor in a model adjusted by consumption of all nutrients [17].

In different studies, dietary fiber intake was negatively associated with the risk of developing GD. In a follow–up study in men from Zutphen [19], total fiber intake acted as a protective factor. In a study carried out in Spain, cases consumed less fiber than controls, and this difference was greater in women [7]. In a study of women from Italy, fiber intake was considered a protective factor [10]. In a more recent study, the association was stronger with an insoluble fiber intake [20].

Calcium acted as a protective factor in men, when comparing higher with lower intakes [19]. In women, calcium intake was lower in cases than controls [7]. In the same study, magnesium and folates were less consumed by GD cases than controls. In Germany, a 7.8% prevalence rate of GD was found in the general population, while in the group of subjects who took vitamin C supplements, the prevalence was 4.7%. When making the risk analysis, vitamin C supplements acted as a protective factor [21]. In a study from Spain [7], vitamin C was less consumed by women in cases than controls.

Objectives

The aim of our study was to compare the different food groups, macronutrients, and micronutrients' average intakes in cases and controls, and to compare those intakes with the recommended dietary allowance, estimating the risk of developing a GD according to those consumptions.

Materials and methods

Study design

A retrospective analyticcase–control study was conducted, nested to a transversal prevalence study carried out between 1989 and 1993 in Rosario City (Argentine) [4].

Since the population composition did not change according to the last censuses carried out and recent prevalence studies were not carried out either, we base our findings on the mentioned study.

Study groups

Subjects with Gallbladder Stones (GS) or who have had a cholecystectomy due to a GS were defined as patients with GD. In this investigation, the case group includes subjects with GD who have participated in our previous prevalence study [4] and who have been contacted and interviewed again; and subjects who have not had the disease at the time of the first study but who at the time of contacted them, years later, it was detected by an ultrasound exam they had developed the disease. Moreover, the control group included a random subsample of subjects who had participated in the previous study, and whose ultrasound results were negative. These patients underwent a new ultrasound of the upper abdomen, in a fasting state, in dorsal, left ventral, and a standing position, with a high–resolution scan, to rule out silent gallbladder stones that could have developed over time since the first study. The sample size was estimated according to the previous prevalence study. A 1-to-1 ratio was used.

All ultrasounds were done by the same diagnostic imaging specialist in the same institution, reducing the possibility of bias in the diagnosis.

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Data collection techniques and instruments

All subjects were interviewed to record demographic data, including age, sex, weight, height, smoking habits, social status, presence of diseases, fluid intake, number of meals per day, vitamin and mineral supplements, antacids, and laxative consumption. Native nationality of parents and grandparents were also inquired.

Body Mass Index (BMI) was calculated by the formula of weight over height squared, and a BMI of 25 to 30 was considered overweight, while a BMI ≥ 30 was considered obese.

Dietary measurements

Quality and quantity of food consumption together with other factors linked to diet were collected in a 210–itemsemi–quantitative Food Frequency Questionnaire (FFQ), validated by an Argentine research group [22]. The FFQ is the most appropriate method for obtaining food data in an epidemiological study, and being considered an important methodological tool for nutritional epidemiology [23]. Food portion size was determined by using a photographic atlas of standardized portions, which was developed by the same Argentinean working group [24], describing the size as small, medium, or large.

Calculations of an average amount of each food were estimated using specialist software developed by the same Argentinean research group. It is important to note that the software calculates food consumption according to the seasonal classification of vegetables and fruits. Food was clustered according to their origin to estimate the average daily intake of each of the food groups in cases and controls. Using the same software we were allowed to determine the energy intake expressed in kilocalories (kcal) [25]. Fruits and vegetables were classified into subtypes according to their nutritional principles. This classification has already been used in previous epidemiological studies [26] and matches the requirements of our study.

Statistical analyses

Measurable variables corresponding to general features from cases and control groups were summarized as means ± standard deviations, while categorical variables were summarized using absolute and relative frequencies (percentages).

Student's *t*–test (to assess continuous variables) andchi–square tests (to assess categorical variables) were used to compare general features.

Crude average daily consumption and standard deviation were calculated for each food group. Moreover, means and standard errors of consumption for each food group adjusted by energy intake, were also calculated. Statistical significance for differences between cases and control groups was assessed by applying general linear models.

Additionally, multiple logistic regression models were used to assess whether there was a lower or higher risk of developing GD when consumption of a particular food increased. The association between dietary factors and GD was based on the relative risks estimated by Odds Ratios (OR), and the statistical significance was evaluated by p - values and 95% Confidence Intervals (CI).

Odds ratios were calculated by dividing the sample into consumption tertiles. Data were arranged in sequential order, from lowest to highest, setting the first tertile as a 'low', the second as a 'moderate' and the third as a 'high' consumption. OR was determined for each consumption tertile, and the lowest consumption tertile was used as a reference category. In order to avoid the confounding effect of descriptive variables whose differences between cases and control groups were significant, they were included in a multiple logistic regression model. As most nutrients were correlated with total energy intake, an adjustment was made to avoid the confounding effect of this variable, thus allowing to detection of the effect of dietary interventions. Disease risk analysis was based on isoenergetic principles [27].

All statistical analyses were conducted by using the STATA statistical software package, version 6.0.

Ethical considerations

The project was reviewed and approved by the Ethics Committee of the School of Medicine, National University of Rosario (FCM/UNR #1123/2011). The investigation was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Prior to their inclusion in the study, written informed consent was obtained from all participants.

Results

The sample size of this study was composed of a total of 120 participants (n = 120). There were 51 subjects (42.5%) in the case-group and 69 (57.5%) in the control group. Forty–three participants who had the disease in the prevalence study were contacted, along with 77 participants who did not present the disease at that time, but when performing an ultrasound, 8 new cases were detected becoming part of the case group (Supplementary Material 1).

No differences were found for sex between cases and controls (p = 0.74). The mean age in cases was 50.65 years while in controls was 53.28, with no statistically significant differences (p = 0.34). Both groups, cases, and controls, were homogeneous in relation to the social status (p = 0.2) and to the ethnicity of grandparents (p = 0.58). No differences between cases and controls were found in relation to smoking, classifying participants as non–smokers, light smokers, mild smokers, and heavy smokers (p = 0.752). When analyzing the number of daily meals, statistically significant differences were found between cases and controls (p = 0.025), being lower in the cases group.

The mean BMI was 28.1 ± 6.02 kg/m² in cases and 26.7 ± 6.25 kg/m² in controls (p = 0.22). Significant differences were found (p = 0.015) when clustering categories into low and normal weight against those indicated as overweight

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(overweight and obesity), observing overweight in 68.6% of cases and in 46.4% of controls.

Regarding the average daily energy intake, statistically significant differences were found between cases and controls (p = 0.002). In the cases group, the average intake was 3218.2 kilocalories a day, while in controls it was 2659.8 kilocalories a day.

Crude and adjusted by Total Energy Intake (TEI) average daily consumption differences between cases and controls, from different food groups, are shown in Table 1. Differences in consumption of nutrients, crude and adjusted by Total Energy Intake (TEI), are shown in Table 2. It was found that the cases group was characterized by higher intakes of total fats, chicken with skin, sausages, and cold cuts. However, the control group was characterized by a statistically significant higher consumption of other vegetables, red and yellow vegetables, total vegetables, other fruits, total fresh fruits, nuts, chicken without skin, skimmed dairy products, total dairy products, and coffee. After being adjusted by TEI, proteins, that were more consumed by controls, as well as fats and oils along with monounsaturated fatty acids, that were more consumed by cases, showed statistically significant differences. Total and insoluble fibers were more consumed by controls, while soluble fiber was more consumed by cases. When adjusting for total energy intake, results were not statistically significant, except for insoluble fiber.

Regarding mineral intake (Table 3), when adjusting by the total energy consumed, calcium and phosphorus were more consumed by controls than cases, with statistically significant results. Likewise, when adjusting by total energy consumed, A and K vitamins were more consumed by controls than cases, as shown in Table 4.

Risk analysis

A multiple logistic regression model was used according to different food groups, macro and micronutrients with soluble and insoluble fibers in consumption tertiles, adjusted by TEI, sex, and other significant variables from the sample. Results with a significant association are shown in Table 5.

Red and yellow vegetable intake reduced GD risk by 96,3% (OR = 0,037) when comparing the highest consumption with the lowest. The highest intakes of nuts also behaved as a protective factor in relation to the lowest tertile. Subjects, who consumed more than 3.9 g of nuts per day had an 80% lower risk of developing the disease, in relation to those who did not consume this product. Fatty cattle meat was a risk factor when comparing the highest intakes with the lowest. Participants who consumed more than the limit of the third tertile (71.6 g) had an increased risk by 18, respectively than those who consumed a lower value to the upper limit of the first tertile (26.1 g). Chicken with skin consumption resulted in a risk factor when comparing higher intakes with the mean and lower. Subjects who consumed more chicken with skin (more than 59.6 g) had an increased risk by 8.4 than those who consumed less. Those who had a mean consumption (< 59.6 g) had an increased risk by 10.6 than those who had a lower consumption.

In the multiple regression models for total fat, when comparing the third tertile with the first one, the OR was 7.959, CI (95%): 1.377–46.014, p – value: 0.0205. In this sense, it is observed that lipid intake is a risk factor and people who consume more than 131 g a day are eight times at higher risk than those who consume 89.5 g or less daily.

Phosphorus intake in the middle third as in the highest, decreases the risk by 91% and 94%, respectively, when compared with the lowest intakes. The number of meals also acted as a protective factor.

GD risk for those subjects who consumed 5 or more meals per day is 84% lower than the corresponding risk for those subjects who consumed 3 or fewer meals. Women had 5 more times the risk of developing the disease than men.

Also, caloric intake was a risk factor. For every single excess of one calorie consumed daily, the risk is increased by 0.1%, that is, for every 100 kilocalories daily consumed, the risk increases by 12%. This variable was considered in the continuous models.

Discussion

Our findings are consistent with those published previously by other authors with different study populations, increasing the evidence that supports descriptive epidemiology suggesting that environmental factors characterizing the development and western modern cultures might be responsible for developing most cholesterol stones.

Regarding the general characteristics of the sample, cases were only differentiated from controls by both the BMI and number of meals, while the remaining variables resulted in similarities in both groups, reaching a strong homogeneity between them. According to our results, the ethnic burden seemed to have little influence on the development of this disease, since no differences were observed from different ethnic groups between cases and controls. This was expected in a country like ours with an important mix of ethnic groups. As the sample is homogeneous in this aspect, the ethnic burden effect is reduced to a minimum.

Consumes in the cases group compared with those in the control group were strongly opposite, the first one presented statistically significant higher intakes of total fats, chicken with skin, and sausages and cold cuts, while the second one presented higher intakes of vegetables, fruits, nuts, chicken without skin, total and skimmed dairy products, and coffee. From this find, it can be gambled a very dissimilar consumer trend between one group and the other.

There are few studies analyzing differences in food consumption prior to carrying out risk analyses. Acase–control study carried out in Spain, showed similar results, GD cases had a higher intake of fats and oils but a lower intake of fruits than controls [7]. In another case–control study from Greece conducted on women, GD cases had a lower intake of fruits but a higher intake of potatoes and corn than controls [14].

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Table 1: Average consumption of food groups.

Food Groups (g)	Group	Crude Mean	Standard Deviation	*p* – value	TEI Adjusted Mean	Standard Error	*p* – value
Fatty Cattle Meat	Controls	51.98	72.39	0.006	65.48	6.54	0.478
	Cases	91.07	78.81		72.80	7.66	
Lean Cattle Meat	Controls	52.56	61.46	0.117	54.24	6.41	0.058
	Cases	37.27	36.77		34.99	7.50	
Cattle Meat	Controls	104.54	91.12	0.141	119.72	7.77	0.33
	Cases	128.33	80.96		107.79	9.10	
Pork Meat	Controls	10.16	24.44	0.745	10.71	2.63	0.529
	Cases	8.87	16.57		8.11	3.08	
Fish	Controls	22.54	25.98	0.215	21.98	2.83	0.369
	Cases	17.21	18.51		17.97	3.32	
Chicken with Skin	Controls	26.22	52.19	< 0.001	29.08	8.44	< 0.001
	Cases	90.97	87.67		87.11	9.88	
Chicken without Skin	Controls	106.28	107.57	< 0.001	111.80	10.57	< 0.001
	Cases	39.09	52.70		31.63	12.38	
Chicken	Controls	132.50	104.50	0.889	140.88	10.86	0.197
	Cases	130.06	77.91		118.74	12.71	
Whole Dairy Products	Controls	110.75	147.10	0.477	119.80	15.55	0.117
	Cases	93.48	105.70		81.24	18.20	
Skimmed Dairy Products	Controls	235.49	215.01	0.012	240.59	25.69	0.007
	Cases	136.41	202.01		129.51	30.08	
Total Dairy Products	Controls	346.24	219.39	0.004	360.39	25.21	< 0.001
	Cases	229.90	201.83		210.75	29.51	
Sausages and Cold Cuts	Controls	34.50	30.42	0.007	37.13	5.38	0.027
	Cases	59.63	59.11		56.07	6.30	
Offal	Controls	3.10	10.43	0.05	3.86	1.23	0.295
	Cases	6.91	10.41		5.89	1.44	
Eggs	Controls	14.88	13.12	0.232	16.02	1.97	0.691
	Cases	18.81	20.42		17.26	2.30	
Corns, pastas and grains	Controls	216.22	102.96	0.001	232.43	10.54	0.108
	Cases	281.22	111.84		259.29	12.34	
Sugar	Controls	11.66	16.30	0.042	13.35	2.30	0.268
	Cases	19.68	23.86		17.38	2.70	
Sweets, sugars, candies and desserts	Controls	66.72	46.30	0.131	73.17	6.26	0.859
	Cases	83.65	68.57		74.92	7.33	
Alcoholic Drinks	Controls	108.27	141.29	0.624	115.67	15.19	0.228
	Cases	96.78	103.75		86.77	17.78	
Sugary Drinks	Controls	116.43	223.44	0.077	143.58	35.34	0.413
	Cases	225.87	391.73		189.15	41.37	
Coffee	Controls	97.41	101.53	0.111	102.23	12.43	0.035
	Cases	66.95	104.35		60.43	14.56	
Herbal Teas	Controls	377.35	313.27	0.434	389.89	32.68	0.184
	Cases	338.24	196.22		321.28	38.26	
Vegetable Oils	Controls	11.08	6.93	0.03	12.03	1.22	0.19
	Cases	15.83	14.06		14.55	1.42	
Animal Fats	Controls	12.45	19.01	0.007	15.13	2.31	0.166
	Cases	23.79	24.44		20.17	2.70	
Total Fats	Controls	23.53	19.43	< 0.001	27.15	2.39	0.046
	Cases	39.61	29.23		34.72	2.80	
Other Vegetables	Controls	62.63	54.11	0.103	65.68	5.57	0.021
	Cases	49.29	34.48		45.16	6.52	
Green Leafy Vegetables	Controls	85.38	78.60	0.886	87.65	8.73	0.599
	Cases	83.49	60.38		80.42	10.22	
Potatoes	Controls	49.83	46.95	0.181	55.89	8.98	0.735
	Cases	68.89	104.34		60.68	10.51	
Coles	Controls	22.44	44.93	0.421	22.31	4.90	0.467
	Cases	16.50	31.57		16.68	5.74	
Red and Green Vegetables	Controls	224.77	143.63	0.001	230.84	15.22	<0.001
	Cases	150.47	96.63		142.26	17.82	
Total Vegetables	Controls	445.05	249.19	0.069	462.37	26.43	0.006
	Cases	368.63	187.70		345.20	30.94	
Other Fruits	Controls	166.45	187.11	0.05	172.90	18.99	0.025
	Cases	113.87	100.07		105.13	22.23	
Fruits Rich in Vitamin A and C	Controls	105.99	141.24	0.334	115.69	14.54	0.058
	Cases	84.99	95.98		71.87	17.02	
Total Fresh Fruits	Controls	272.44	280.15	0.105	288.60	29.01	0.016
	Cases	198.86	183.72		177.0	33.96	
Nuts	Controls	2.18	3.54	< 0.001	2.16	0.35	0.002
	Cases	0.41	1.29		0.43	0.41	
Leguminous Vegetables	Controls	7.92	10.10	0.518	7.74	1.23	0.687
	Cases	6.72	9.95		6.96	1.44	

g: Grams; TEI: Total Energy Intake.

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Table 2: Averages consumption of nutrients.

Nutrients	Group	Crude Mean	Standard Deviation	*p* – value	TEI Adjusted Mean	Standard Error	*p* – value
Carbohydrates (g)	Controls	297.62	91.59	0.013	319.96	6.92	0.702
	Cases	346.03	119.66		315.80	8.10	
Proteins (g)	Controls	116.83	38.56	0.358	124.70	2.63	0.004
	Cases	123.25	36.40		112.60	3.08	
Fat and oils (g)	Controls	104.26	47.53	0.000	116.44	2.49	0.028
	Cases	141.64	57.67		125.17	2.92	
Monounsaturated fatty acids (g)	Controls	39.92	21.30	0.000	44.94	1.32	0.037
	Cases	56.10	24.01		49.30	1.54	
Polyunsaturated fatty acids (g)	Controls	15.50	8.60	0.001	17.07	0.78	0.092
	Cases	21.27	9.12		19.15	0.91	
Saturated fatty acids (g)	Controls	42.59	21.51	0.000	47.85	1.39	0.054
	Cases	59.21	26.13		52.10	1.63	
Cholesterol (mg)	Controls	409.74	192.48	0.008	448.24	17.15	0.662
	Cases	512.14	222.89		460.06	20.08	
Soluble Fibres (g)	Controls	5.73	2.32	0.408	6.09	0.23	0.182
	Cases	6.09	2.36		5.61	0.27	
Insoluble Fibres (g)	Controls	16.51	7.06	0.453	17.18	0.78	0.041
	Cases	15.55	6.63		14.64	0.92	
Alcohol (g)	Controls	10.81	15.66	0.684	11.70	1.64	0.225
	Cases	9.77	10.74		8.56	1.92	
Total Fibres (g)	Controls	22.23	9.12	0.718	23.26	0.99	0.053
	Cases	21.64	8.75		20.25	1.15	

TEI: Total Energy Intake; g: Grams; mg : Miligrams.

Table 3: Averages consumption of minerals.

Minerals	Controls/ Cases	Crude Mean	Standard Deviation	p – value	TEI Adjusted Mean	Standard Error	*p* – value
Iron (mg)	Controls	20.65	6.48	0.087	22	0.56	0.288
	Cases	22.87	7.59		21.06	0.66	
Calcium (mg)	Controls	1088.06	488.81	0.122	1139.16	54.21	0.003
	Cases	948.78	477.37		879.64	63.45	
Phosphorus (mg)	Controls	1666.97	466.88	0.941	1765.22	37.30	< 0.001
	Cases	1673.68	523.09		1540.75	43.67	
Selenium (µg)	Controls	114.32	40.69	0.473	119.49	4.92	0.424
	Cases	120.28	49.89		113.29	5.76	
Zinc (µg)	Controls	11113.78	4677.33	0.793	11717.45	546.83	0.174
	Cases	11358.22	5488.23		10541.49	640.11	

TEI: Total Energy Intake; mg = Milligrams; µg = Micrograms.

Table 4: Average consumption of vitamins.

Vitamins	Controls/ Cases	Crude Mean	Standard Deviation	*p* – value	TEI Adjusted Mean	Standard Error	*p* – value
Vitamin A (µg)	Controls	3373.79	2645.34	0.064	3492.36	280.65	0.016
	Cases	2570.32	1803.62		2409.90	328.52	
Vitamin B1 (mg)	Controls	1.31	0.45	0.266	1.40	0.04	0.067
	Cases	1.40	0.51		1.29	0.05	
Vitamin B2 (mg)	Controls	2.29	0.87	0.283	2.46	0.10	0.300
	Cases	2.51	1.31		2.29	0.12	
Vitamin B5 (mg)	Controls	22.92	8.53	0.026	24.51	0.81	0.972
	Cases	26.69	9.75		24.55	0.95	
Vitamin B6 (mg)	Controls	1.60	0.56	0.147	1.68	0.07	0.983
	Cases	1.77	0.68		1.67	0.08	
Vitamin C (mg)	Controls	234.09	142.95	0.260	253.04	18.16	0.725
	Cases	268.63	191.49		242.99	21.26	
Vitamin E (mg)	Controls	8.67	4.31	0.739	9.15	0.51	0.280
	Cases	8.95	4.79		8.29	0.59	
Vitamin K (mg)	Controls	979.44	461.09	0.887	1046.31	40.72	0.024
	Cases	990.56	364.17		900.09	47.67	

TEI: Total Energy Intake; µg = Micrograms; mg = Milligrams.

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Table 5: Odds Ratios (OR) and 95% confidence interval (CI) estimated using a multiple logistic regression model.

	OR	95% CI	*p* – value
Red and Yellow Vegetables (3rd tertile *vs.* 1st tertile)	0.037	0.006 – 0.230	0.0004
Nuts (3rd tertile *vs.* 1st tertile)	0.201	0.053 – 0.769	0.0190
Fatty Cattle Meat (3rd tertile *vs.* 1st tertile)	18.163	2.270 – 145.292	0.0063
Chicken with Skin (2nd tertile *vs.* 1st tertile)	10.595	2.038 – 55.094	0.0050
Chicken with Skin (3rd tertile *vs.* 1st tertile)	8.435	2.069 – 34.394	0.0029
Total fats (3rd tertile *vs.* 1st tertile)	7,959	1,377 – 46,014	0,0205
Phosphorus (2nd tertile *vs.* 1st tertile)	0.086	0.020 – 0.371	0.0010
Phosphorus (3rd tertile *vs.* 1st tertile)	0.055	0.008 – 0.385	0.0035
Kilocalories	1.001	1.000 – 1.002	0.0077
Number of meals (5 or more meals *vs.* 3 or fewer meals)	0.16	0.030 – 0.856	0.0322
Sex (Women *vs.* Men)	5.353	1.284 – 22.326	0.0213

In our study, Red and yellow vegetables also showed a protective effect at the risk of developing GD, when comparing highest with lowest intakes. The intake that protects against GDs is more than 11 moderate servings per week when compared to participants who consumed these products in the same serving size, but 6 times per week or less. Related to these findings, we found two publications reporting this association, although both are studies with a different design to ours. In a follow–up research from the United States conducted on women, applying a multivariate analysis of fruit and vegetable total intakes, when comparing the highest with the lowest quintile of consumption, it emerged that fruit and vegetable consumption behaved as a protective factor for cholecystectomy. When classifying food groups, the protective factor was maintained with statistical significance in total fruits, total vegetables, green leafy vegetables, citrus fruits, and vegetables and fruits rich in vitamin C [13]. In a recent cohort study from Sweden, in an age–and–adjusted analysis, fruit and vegetable intake was found inversely associated with cholecystectomy risk. However, when conducting a multivariate analysis considering confounding factors, that effect lost statistical significance. When classifying these major food groups into total fruits, total vegetables, citrus fruits, green leafy vegetables, cruciferous vegetables, and vegetables rich in vitamin C, no statistical significance was found. Nevertheless, an interaction between age and total fruit with vegetable intakes was found in women less than 60 years, and when analyzing the risk in the highest quartile intake compared with the lowest, this intake behaved as a protective factor [28]. In relation to red and yellow vegetables confirmed for this study, all of them are rich in beta carotene, precursors of vitamin A. In research where antioxidant differences were studied between patients with cholesterol stones and controls, in order to verify the role of such minerals and vitamins as cofactors of key enzymes in a hepatic metabolic process of bilirubin and cholesterol, beta carotene plasma values were found as statistically significantly higher in controls than in cases [29]. In a previous study carried out by the same research group, it was found that patients with GD consumed less than 10 of the 16 antioxidants containing beta carotenes studied [30]. Vitamin C, which is found in that group of vegetables, might also be a protective factor for developing GD. In a study from Germany, the authors have found a lower prevalence of GD in subjects who consumed supplements of vitamin C compared with the general population; and when analyzing the risk, vitamin C supplement intake behaved as a protective factor [21]. The mechanism whereby this water–soluble vitamin could act as protective might be due to the fact that it influences the activity of 7–α–hydroxylase in the gall, reducing the lithogenic risk in adults [2,31].

By performing risk analysis in food groups, it was found nut intakes had a protective effect in patients at risk of developing a GD when comparing the highest with the lowest consumption tertile. However, it is worth mentioning that intake that would protect against this illness is very low, less than 3 almonds every 8 days, or 2 walnuts every 20 days, in comparison with those who never consume this kind of food. This effect was also found by other authors in two cohorts–studies conducted in women and men in the United States. In those studies, a multivariate analysis was made to compare subjects who consumed 5 or more servings of nuts with those who rarely consumed them [15,16]. Mechanisms of this possible beneficial effect could be various. Certain minerals and fibers could be more powerful and may act as a protective mechanism. In a study from Italy, fiber intake was associated with a lower risk of GD in women [10]. In a follow–up study from the United States, also conducted in women, total fiber acted as a protective factor. When analyzing separately soluble and insoluble fiber, soluble fiber lost statistical significance while insoluble fiber showed a more pronounced protective effect than the total fiber, consequently soluble fiber intake was integrated into the multivariate model [20]. The protective effect of insoluble fiber intake might be a result of an acceleration of intestinal passage, with the subsequent reduced formation of deoxycholic acid and the increased formation of chenodeoxycolic acid by intestinal bacteria. In that way, deoxycholic acid decreases, which would be involved with an increase of cholesterol saturation in the gallbladder, while chenodeoxycolic acid decreases the lithogenicity, being therapeutically used to promote dissolution of gallstones [2,32]. Magnesium and calcium are minerals contained in nuts, . In a follow–up study conducted in men, , when comparing the highest quintile of consumption with the lowest, the total intake of magnesium (dietary and supplements) was considered in an adjusted model by total energy and other confounder factors, magnesium intake behaved as a protective factor [33]. A possible reason for this effect may be the magnesium deficit associated with dyslipidemia and hypersecretion of insulin, which may contribute to the formation of gallstones [33,34]. In a study from the Netherlands conducted in men, calcium also behaved as a protective factor at the risk of developing GD [19]. Calcium intake in dietary causes a decrease in the cholesterol saturation in the gallbladder, through a preventive resorption of secondary bile acids in the colon [2].

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Fatty cattle meat cuts and chicken with skin behaved as risk factors. One and a half moderate portion a week intake of chicken with skin increased GD risk when compared with no consumption of this food. Regarding fatty meat intake, the risk increased when consuming more than 5 moderate portions per week, compared with those who consumed these cuts less than 2 times per week. Although there were no results where these findings could have been found, all of those kinds of food are fat sources, particularly, saturated fats. In a French study [8], total fats were found as GD risk factors. In Italy [17], saturated fat was found as a risk factor, while in the United States [18] only saturated long-chain fatty acids behaved as risk factors when comparing in a multivariate analysis the highest with the lowest quintile of intake [18].

About macronutrients, in the risk analysis, adjusted for the total energy consumed, when comparing the highest consumption tertile with the lowest, total fat intake acted as a risk factor. The limiting values that set the increase in risk were ≥131g, which means an intake of≥2 g per kg of body weight, compared with intakes 90≤g which represents between 1 and 1.3g per kg of body weight. These findings are similar to results found by other authors, in which total fats [8] and saturated fats [17] were found as risk factors. In another paper, only long–chain saturated fatty acids reacted as risk factors when comparing the highest intake quintile with the lowest, in a multivariate analysis [18]. It is clear that fats have been widely studied due to their relation to the development of gallstones. From older studies, fats were positively associated with an increased incidence in countries such as Japan [35] and Saudi Arabia [36], and more recently, in studies from European countries, with the risk of developing gallstones [8,17]. Although total fats were the most studied, when classifying them it seemed that the effects produced on the stone formation would not be the same, depending on the type of fatty acid involved. In this sense, the results are not conclusive. While monounsaturated fatty acids were most consumed by cases in the study from Spain [7], the study from Italy performed a protective effect [17].

Within micronutrients, phosphorus behaved as a protective factor at risk of developing a GD. It should be noted that intakes that acted as a protective factor exceeded the recommendations. Furthermore, due to phosphorus is a mineral widely distributed in foods and is used in the elaboration of food products, its intake has increased in most populations, exceeding the recommendations. It is possible that with calcium our results were not significant since intakes did not reach recommendations, except for men in controls.

Acase–control study of GD [30] comparing antioxidants intake and assessing the effect on the action of enzymes involved in the bilirubin and cholesterol metabolism, found that patients with gallstones had lower phosphorus intakes. In the same study, calcium was also less consumed by cases, which was similar to what happened in our sample, although no significant results were found for this mineral in the risk analysis.

The number of daily meals was higher in controls, with statistically significant results. This means that in some cases, subjects would be making heavier meals and at greater intervals throughout the day, having longer periods of fasting. When making risk analysis in the model analyzing micronutrients and all adjusted variables, the number of meals was a protective factor. Subjects who consumed 5 or more meals per day were protected by an 84% risk of developing a GD when comparing with those who consumed 3 or fewer meals per day. There are recommendations indicating making a higher number of meal intakes at regular intervals might reduce the risk of developing a GD since it prevents biliary stasis and reduces lithogenesis in the gall [2,37]. There are two studies showing similar results to ours. The first one is acase–control study from Spain, where GD cases made fewer meals per day, overlooking afternoon tea and dinner [7]. The second study, the MICOL project (Multicenter Italian Study on Epidemiology of Cholelithiasis) from Italy, showed that short overnight fasting was a protective factor at risk of developing the disease in both sexes [10].

In the model analyzing micronutrients, kilocalories behaved as a risk factor. This variable was considered continuous and consequently, the OR was very small, meaning that it accounts for an increase in the risk for every 1 kilocalorie that increases the TEV. If we consider an increase of 100 kilocalories in the TEV, the increased risk will be 12%. In other studies [7,8,9] from different countries, the same association was found, but such studies are poor. In research from Italy [10], a negative association was found between energy intake and the risk of developing a GD in men. Although the hypothesis suggesting high–high-calorie diets are correlated with low–density nutritional foods, carbohydrates and refined fats intake, low–fiber intake, and low vitamin and minerals intake, this is not a risk factor that has been proved in many studies. This causes an increase in overweight and obesity, as well as metabolic syndrome, pathologies that have proved to be lithogenics due to increased cholesterol synthesis and its secretion, increasing the risk of developing a GD [6].

Finally, the already determined risk factor of belonging to the female gender was confirmed [2,38], since it was statistically significant in the risk model analysis.

Conclusion

We can conclude that certain general aspects that prevent multiple chronic diseases, such as maintaining a healthy body weight and eating a balanced diet, decrease the risk of developing GD. Therefore, promoting healthy eating habits, focusing on reducing fats and oils, selecting lean meat cuts and removing skin from the chicken, increasing fruits and vegetables intake, mainly those reds and yellows in at least two daily servings, consuming dairy products every day, and incorporating nuts intake to regular diet at least once a week, might help to reduce the risk of developing GD.

Authors contributions

Designed research: ABC, SMP; Conducted research: ABC, HAP, SMB, SMP; Manuscript writing: ABC, HAP, SMP.

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(Supplementary Material)

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