Evaluation of Factors Affecting the Type of Gallstone

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Abstract The aim of this study is to determine the factors affecting the formation of the gallstone types of cholesterol and pigment stones. This descriptive and retrospective study comprised 164 patients who underwent cholecystectomy. Research data were obtained using a data collection form with 34 questions developed by the researchers based on the relevant literature. Statistical analysis of the data was made on SPSS 15.0 software using the percentage assessment method and chi-square test. Advanced statistical analysis of the data was performed using multivariate logistic regression. Cholesterol stone was found to form in individuals with anemia, those going through the menopause, and those consuming liquid oil and not undertaking exercise. The risk of pigment stone formation was found to be higher in the obese and those with liver disease and who do not consume milk. From the results of the study, it was determined that the dietary habits, chronic diseases, and lifestyle behaviors of individuals could be effective factors in the formation of cholesterol and/or pigment stone.

Keywords Gallstones · Cholecystectomy · Lifestyle · Nutrition

Introduction

With a varying prevalence in different countries, gallstone (GS) is an important cause of morbidity throughout the world. It has been reported that the increase in the incidence of gallstone, which is frequently seen between the ages of 50 and 65 years, is related to longer life expectancies and changes in dietary habits [1].

The main elements in the structure of gallstones, which can be classified into two groups as cholesterol and pigment stones, are bile pigment and calcium. Various other elements such as iron, phosphorus, carbonate, protein, carbohydrates, mucus, and cellular debris can also be found [2, 3].

Factors reducing the normal storage function and motility and causing the formation of “cholesterol stone” can be listed as age, obesity, weight loss, multiparity, hyperlipidemia, diabetes mellitus, high-calorie diets, and medications used [4–7].

Involving calcium bilirubinate as a dominant component, the “pigment stones,” which account for 30 % of gallstones, are divided into black pigment and calcium bilirubinate stones. Black pigment stones are tarlike, hard, and shiny stones due to the high content of inorganic components and mucin [2, 8]. Calcium bilirubinate stones are soft, not bright, brown, and malodorous. Cirrhosis, ileal diseases, hemolytic anemia, truncal vagotomy, hyperparathyroidism, and bile duct infections can be listed as the reasons for the formation of pigment stones [9].

Education and raising awareness of dietary habits and lifestyle are crucial as lifestyle and nutrition are primary causes of gallstones. In this sense, nurses have an important responsibility for community education.

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Methods

Approval for the study was granted by the local ethics committee. This retrospective and descriptive study included 223 patients without any diagnosis of malignancy who underwent cholecystectomy surgery in our university hospital between January 2013 and March 2014. Of this initial group, 164 patients met the criteria. Informed consent was obtained from all participants. Data was obtained from the hospital records of the patients.

Further data for the study were obtained through a survey consisting of 34 questions about demographic characteristics (age, gender, education, occupation), lifestyle (alcohol, smoking, sports, medication used), chronic diseases, and dietary habits of the patients participating in the study. The patients were classified into two different groups based on cholesterol or pigment stone development according to the pathology reports.

The data obtained in the study were evaluated using SPSS for Windows 15.0 software (Statistical Package for the Social Sciences—SPSS Inc., Chicago, IL, USA). The statistical analysis was performed through the percentage evaluation method and chi-square test. A multivariate logistic regression model was used for advanced statistical analysis.

The body mass index, sporting activities, anemia, liver disease, milk consumption, oil type, and water consumption were examined, and as a potential mix for the determination of stone types, the multivariate logistic regression model was used. The results were evaluated at 95 % confidence interval, $p < 0.05$ significance level and $p < 0.01$ and $p < 0.001$ advanced significance levels. A nominal two-sided p value was adopted for all comparisons.

Results

Pigment (brown–black) stones were found in 75 (45.7 %), and cholesterol (yellow–green) stones were found in 89 (54.3 %) of 164 patients involved in the study. The demographic characteristics of the patients are shown in Table 1.

Pigment stones were seen in 18.7 % of those with anemia, in 20 % of those with liver disease, in 68.2 % of patients using antihypertensive drugs, in 63.6 % of those on medication for more than 6 years, and in 17.9 % of patients using oral contraceptives. Cholesterol stones were seen in 31.5 % of those with anemia, in 4.5 % of those with liver disease, in 38.2 % of patients using antihypertensive drugs, and in 41.2 % of those on medication for 1–3 years, and not seen in any patient using oral contraceptive.

In Table 3, there is no significant difference between the formation of cholesterol or pigment stones and the weekly consumption of meat, day-fresh egg and water, and the place of birth ($X^2 = 7.506$, $p = 0.057 > 0.05$; $X^2 = 0.001$, $p = 0.582 >$

0.05 ; $X^2 = 0.172$, $p = 0.403 > 0.05$; $X^2 = 0.487$, $p = 0.296 > 0.05$, respectively). Twenty percent of pigment stone cases and 32.6 % of cholesterol stone cases consume milk every day, and a significant difference is seen between the two stone types ($X^2 = 3.283$, $p = 0.050 < 0.05$). While 29.3 % of the pigment stone cases use olive oil and 9.3 % use butter, 7.9 % of the cholesterol stone cases use olive oil and 24.7 % use butter, so there is a statistically significant difference ($X^2 = 18.326$, $p = 0.000 < 0.05$). A statistically significant difference is seen between pigment and cholesterol stones in terms of sporting activities ($X^2 = 4.991$, $p = 0.019 < 0.05$). Pigment stone was determined in 53.3 % of those undertaking sporting activities, and cholesterol stone was determined in 64 % of those who did not do any sports.

When adjusted odds ratio (OR) of the potential mixing factors for the determination of gallstone types is calculated, the pigment stone risk according to body mass index is OR 5.01 (95 % CI 1.60–15.66, $p = 0.006$) in obese patients, OR 10.66 (95 % CI 3.18–35.73, $p = 0.000$) in those with no sporting activity, OR 10.90 (95 % CI 2.81–42.26, $p = 0.001$) in people with liver disease, and OR 6.82 (95 % CI 2.15–21.68, $p = 0.001$) in those who do not consume milk every day.

The cholesterol stone risk is higher in people with anemia [OR 3.21 (95 % CI 1.04–9.92), $p = 0.043$] and women in the menopause period [OR 3.34 (95 % CI 1.40–7.93), $p = 0.006$] compared to women with ongoing fertility.

The risk of cholesterol stone is much higher in cases consuming liquid oil compared to cases consuming olive oil [OR 13.92 (95 % CI 3.50–55.41), $p = 0.000$] and in cases consuming butter comparing to cases consuming olive oil [OR 319.93 (95 % CI 30.24–3385.36), $p = 0.000$]. The risk of cholesterol stone is higher in people consuming liquid and olive oil together comparing to those consuming only olive oil [OR 5.21 (95 % CI 1.27–21.35), $p = 0.022$]. In addition, it was determined that water consumption was not a mixing factor in terms of the stone type.

Discussion

Although the prevalence varies by country, age, female gender and genes are considered unchangeable factors and obesity, rapid weight loss, drugs and physical activity/lifestyle are considered changeable factors in gallstone, which is one the most common diseases in the world and in our country and develop based on multifactorial reasons [10, 11].

The age range specified as 50–65 years for the highest incidence supports the age range of 50 years and over that was obtained in the current study [12] (Table 1). In community-based studies performed in countries where gallstone disease is common, the disease has been reported at a higher rate in females than in males. This reveals that estrogens and/or progestins displayed a lithogenic effect [13].

Table 1 Comparison of stone types and demographic characteristics of patients with cholecystectomy ($n=164$)

Demographic data		Pigment stone		Cholesterol stone		p
		n	%	n	%	
Age (years)	≤30	11	14.7	18	20.2	$\chi^2=1.292, p=0.731$
	31–40	17	22.7	21	23.6	
	41–50	26	34.7	25	28.1	
	≥51	21	28.0	25	28.1	
Gender	Female	42	56.0	61	68.5	$\chi^2=2.740, p=0.068$
	Male	33	44.0	28	31.5	
Education level	Primary education	4	5.3	20	22.5	$\chi^2=10.012, p=0.007$
	Secondary—high school	30	40.0	33	37.1	
	University and above	41	54.7	36	40.4	
Hometown region	Marmara	20	26.7	12	13.5	$\chi^2=27.232, p=0.000$
	Aegean	3	4.0	6	6.7	
	Mediterranean	4	5.3	2	2.2	
	Black Sea	14	18.7	28	31.5	
	Eastern Anatolia	11	14.7	4	4.5	
	Northeastern Anatolia	9	12.0	1	1.1	
	Central Anatolia	11	14.7	24	27.0	
	Immigrant	3	4.0	12	13.5	
Childbirth history	Nulliparous	13	31.0	13	21.3	$\chi^2=1.225, p=0.190$
	Previous live births	29	69.0	48	78.7	
Childbearing age (years)	≤20	9	31.0	6	12.5	$\chi^2=15.103, p=0.001$
	21–25	3	10.3	26	54.2	
	≥26	17	58.6	16	33.3	
Menopause	Present	22	52.4	17	27.9	$\chi^2=6.352, p=0.010$
	Absent	20	47.6	44	72.1	
Family history	None	24	32.0	19	21.3	$\chi^2=12.973, p=0.011$
	Mother	8	10.7	7	7.9	
	Father	0	0.0	4	4.5	
	Sibling	26	34.7	20	22.5	
	Relative	17	22.7	39	43.8	
BMI	Slim	0	0.0	6	6.7	$\chi^2=10.849, p=0.013$
	Normal	22	2.3	30	33.7	
	Overweight	26	34.7	37	41.6	
	Obese	27	36.0	16	18.0	

Significance level: $p<0.05$

Consistent with the results of these studies, the findings obtained in the current study showed that female patients had a higher rate of gallstones and it was seen that there was no statistically significant difference between the types of gallstones (Table 1).

In literature, it has been reported that of the gallstone types, cholesterol stone is more widely observed in the USA, western countries, and Turkey [1, 14]. In the current study, the high rate of cholesterol stone can be considered to be due to dietary habits and increasing age.

Pregnancy leads to various changes in gallbladder functions and gallbladder residual volume increases to double the normal. This explains the increasing frequency of gallstones in fertile women [1]. Mendez et al.

determined that the incidence rate of gallstone in pregnant women was 5–12 % and stated that this ratio increased with the number of pregnancies [15, 16]. In the current study, that the rate of pregnancy-based cholesterol stone was determined to be about three times higher is consistent with results in literature (Table 1) ($p=0.278$).

As the use of conjugated estrogens in premenopausal women and the estrogen practice in postmenopausal women have similar lithologic effects, they are known to be important risk factors in the formation of cholesterol stone. However, in contrast to this view, it was seen in the current study that the pigment stone type was observed more in cases of menopause [17] (Table 1).

In this study, both gallstone types were seen more in those with a family history of gallstone (pigment 68 %, cholesterol 79 %), and a statistically significant difference was found between the stone types in favor of cholesterol stone. Studies performed on families have shown that genetics play a significant role on the formation of gallstone, and the results of those studies can be considered consistent with those of the current study [18] (Table 1).

A relationship has been reported between gallstone and diseases such as diabetes, hemolytic anemia, cirrhosis, and ileum resection. In the current study, there was no significant relationship between the formation of gallstone type and diabetes, hypertension, or heart disease. However, a positive relationship has been determined between diabetes and gallstone in previous researches conducted on diabetic patients [18, 19], and insulin resistance has been defined as a risk factor in the formation of gallstone [19] (Table 2).

High bilirubin levels arising from the destruction of erythrocytes in hemolytic anemia and cholesterol are known to lead to the formation of gallstone [20]. In the current study, the incidence of cholesterol stone was found to be higher in patients with anemia (Table 2).

Yıldırım et al. reported a relationship between pigment stones and liver diseases with prevalence rising to 30 %. Although no biological reason could be definitively

determined, it has been suggested that altered pigment secretion could correlate with increased estrogen levels and/or abnormal gallbladder motility [21]. In the current study, the incidence of pigment stone in patients with liver diseases was found to be higher compared to cholesterol stone, and the result was highly significant statistically, which is consistent with literature data ($p=0.002$) (Table 2).

Reshetnyak et al. showed that oral contraceptives and hormone replacement treatment doubled the incidence of cholesterol stone [22], although Şahin et al. did not support that finding in their study [11]. Estrogen leads to the formation of supersaturated gall by increasing hepatic cholesterol synthesis and reducing bile salt synthesis. The serum progesterone level rises with the use of some oral contraceptives, which can be correlated with inadequate discharge of the gallbladder and increasing residual volume [1, 22, 23]. In the current study, it is thought that the higher incidence of pigment stone in patients using oral contraceptives compared to cholesterol stone was due to the low estrogen dose in oral contraceptives and their short duration of use (Table 2).

In a study by Scragg, Misciagna, and Rautray, the formation of gallstone was associated with lifestyle and dietary habits [24–26]. That there is currently a higher incidence of cholesterol stones than pigment stones, which used to be seen more frequently in Far Eastern countries, can be attributed to

Table 2 Comparison of the chronic diseases and drug use of patients with cholecystectomy and the stone type ($n=164$)

		Pigment stone		Cholesterol stone		<i>p</i>
		<i>n</i>	%	<i>n</i>	%	
Chronic diseases						
Diabetes	Present	6	8.0	5	5.6	$\chi^2=0.369, p=0.382$
	Absent	69	92.0	84	94.4	
Hypertension	Present	17	22.7	11	12.4	$\chi^2=3.054, p=0.062$
	Absent	58	77.3	78	87.6	
Heart disease	Present	3	4.0	3	3.4	$\chi^2=0.046, p=0.575$
	Absent	72	96.0	86	96.6	
Anemia	Present	14	18.7	28	31.5	$\chi^2=3.497, p=0.045$
	Absent	61	81.3	61	68.5	
Liver disease	Present	15	20.0	4	4.5	$\chi^2=9.553, p=0.002$
	Absent	60	80.0	85	95.5	
Drug use						
Drug use	Yes	22	29.3	34	38.2	$\chi^2=1.424, p=0.152$
	No	53	70.7	55	61.8	
The drug used	Antihypertensive	15	68.2	13	38.2	$\chi^2=14.105, p=0.003$
	Antidepressant	5	22.7	2	5.9	
	Stomach	0	0.0	11	32.4	
	Thyroid	2	9.1	8	23.5	
Duration of drug use	Less than 1 year	5	22.7	2	5.9	$\chi^2=18.309, p=0.000$
	1–3 years	3	13.6	14	41.2	
	4–5 years	0	0.0	10	29.4	
	More than 6 years	14	63.6	8	23.5	
Birth control drug use	Yes	7	17.9	0	0.0	$\chi^2=11.773, p=0.001$
	No	32	82.1	61	100.0	

Significance level: $p<0.05$

Table 3 Comparison of the dietary habits and lifestyle of patients with cholecystectomy and the stone type ($n=164$)

Dietary habits		Pigment stone		Cholesterol stone		<i>p</i>
		<i>n</i>	%	<i>n</i>	%	
Weekly meat consumption	1–2 times	35	46.7	35	39.3	$\chi^2=7.506, p=0.057$
	3–4 times	22	29.3	31	34.8	
	5 times and over	18	24.0	16	18.0	
	None	0	0.0	7	7.9	
Milk consumption	Yes	15	20.0	29	32.6	$\chi^2=3.283, p=0.050$
	No	60	80.0	60	67.4	
Egg consumption	Yes	65	86.7	77	86.5	$\chi^2=0.001, p=0.582$
	No	10	13.3	12	13.5	
Oil type	Liquid oil	26	34.7	42	47.2	$\chi^2=18.326, p=0.000$
	Olive oil	22	29.3	7	7.9	
	Butter	7	9.3	22	24.7	
	Liquid and olive oil	20	26.7	18	20.2	
Birth place and response to food culture	Existent	47	62.7	51	57.3	$\chi^2=0.487, p=0.296$
	Nonexistent	28	37.3	38	42.7	
Water consumption	Less than 1 l	23	30.7	30	33.7	$\chi^2=0.172, p=0.403$
	1 l and over	52	69.3	59	66.3	
Lifestyle behaviors						
Alcohol	Uses	8	10.7	13	14.6	$\chi^2=0.566, p=0.304$
	Does not use	67	89.3	76	85.4	
Smoke	Uses	31	41.3	36	40.4	$\chi^2=0.013, p=0.517$
	Does not use	44	58.7	53	59.6	
Sporting activities	Present	40	53.3	32	36.0	$\chi^2=4.991, p=0.019$
	Absent	35	46.7	57	64.0	

Significance level: $p<0.05$

the change in dietary habits in these countries. It has been shown in many epidemiological studies that high intakes of calories, refined carbohydrates, and salt affect the formation of gallstones [23, 27].

Oils are a significant nutritional factor known to lead to the formation of gallstones. It has been shown that cholesterol more than bile acids and phospholipids could be effective in the formation mechanism of gallstones [23]. According to the

Table 4 Comparison of patient characteristics and stone type through multivariate logistic regression analysis ($n=164$)

Potential mixings		Pigment stone		Cholesterol stone		p	B	p	OR	95 % CI for OR	
		n	%	n	%						
Body mass index	Normal	22	29.3	30	33.7	0.013		0.002			
	Thin	0	0.0	6	6.7		−19.157		0.999		
	Overweight	26	34.7	37	41.6		−0.945		0.086	2.57	0.88 7.55
	Obese	27	36.0	16	18.0		1.611		0.006	5.01	1.60 15.66
Positive family history		75	100.0	89	100.0	0.011	−0.520	0.317	1.68	0.61	4.65
No sporting activity		35	46.7	57	64.0	0.019	2.367	0.000	10.66	3.18	35.73
Anemia present		14	18.7	28	31.5	0.045	−1.165	0.043	3.21	1.04	9.92
Liver disease present		15	20.0	4	4.5	0.002	2.388	0.001	10.90	2.81	42.26
No milk consumption		60	80.0	60	67.4	0.050	−1.921	0.001	6.82	2.15	21.68
Oil type	Olive oil	22	29.3	7	7.9	0.000		0.000			
	Liquid oil	26	34.7	42	47.2		−2.633		0.000	13.92	3.50 55.41
	Butter	7	9.3	22	24.7		−5.768		0.000	319.93	30.24 3385.36
	Liquid and olive oil	20	26.7	18	20.2		−1.651		0.022	5.21	1.27 21.35
Water consumption less than 1 l		52	69.3	59	66.3	0.403	−0.603	0.213	1.83	0.71	4.72
Menopause present		22	52.4	17	27.9	0.010	1.205	0.006	3.34	1.40	7.93

Significance level: $p<0.05$

OR Odds Ratio

data obtained in the current study, the incidence of cholesterol stone was higher in patients with a higher rate of weekly meat and milk consumption ($p=0.050$). Both gallstone types were seen in patients with a high rate of egg consumption (Table 3).

In respect of lifestyle, regular and intense physical activity in particular reduces the risk of gallstone in females due to the positive effects on lipid metabolism [28]. Physical activity is also an indicator of body weight, and when undertaken regularly, LDL cholesterol and triglyceride levels decrease, HDL cholesterol levels rise, insulin sensitivity increases, and blood pressure decreases [29]. A high rate of cholesterol stone incidence was found in this study for patients who did not undertake any physical activity, which is consistent with data in literature (Table 3).

The reduction of bile salt and lecithin production in the liver and the increase of cholesterol secretion cause the formation of gallstone in obese patients. Cholesterol is extremely active in these individuals, and bile is excessively saturated with cholesterol in fasting periods, which results in the formation of gallstones [13]. Scragg et al. showed that the risk of gallstone formation in obese women under the age of 50 was higher than in the general population [24]. In the current study, according to BMI, the pigment stone incidence was higher in obese patients [OR 5.01 (95 % CI 1.60–15.66), $p=0.006$] which is consistent with the findings of other studies in this field (Table 4).

One of the first studies which showed a relationship between oils used in foods and gallstone-dependent diseases was a case–control study by Linos et al. in 1989. In that study, it was determined there was a statistically significant ($p<0.05$) positive relationship only with animal fats, of the dietary-dependent factors. Interestingly, there has been reported to be a negative, i.e., protective, relationship between excessive consumption of olive oil and the disease [30].

Olive oil, which increases bile by stimulating gallbladder function, has an effect on the hepatobiliary system of providing optimal absorption of bile secretion and discharging the gallbladder completely (<http://www.internationaloliveoil.org/estaticos/view/95-olive-oil-and-the-digestive-system>). It stimulates bile salt synthesis in the liver, as well as increases the amount of cholesterol discharge. The cholesterol level rises in the blood with the consumption of saturated fats, and it leads to cholesterol stone formation combining with bile pigments. This explains the high risk of cholesterol stone formation in patients consuming butter [OR 319.93 (95 % CI 30.24–3385.36), $p=0.000$] compared to those consuming olive oil in the current study [27] (Table 4).

Conclusion

There are many elements in the formation of gallstone types, such as gender, genetic factors, environmental factors, dietary

habits of individuals, and lifestyles of individuals. While it is not possible to change genetic and environmental factors, the others are preventable and treatable. According to the data obtained as a result of this study, dietary habits and lifestyle are extremely influential in the formation of both gallstone types. Therefore, community education programs on wellness and dietary habits could play a crucial role in reducing the incidence of gallstone.

Conflict of Interest The authors declare that they have no competing interests.

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