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Factors associated with true vesicular polyps in patients with polypoid lesions

Factores asociados a la presencia de pólipos vesiculares verdaderos en pacientes con lesiones polipoides

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ABSTRACT

Introduction: gallbladder pseudo polyps are considered benign lesions, while true polyps are related to the gallbladder's adenoma-adenocarcinoma sequence. **Objective:** to determine if there are sociodemographic or clinical risk factors related to the presence of true gallbladder polyps in patients with polypoid lesions submitted to cholecystectomy in a Third Level Hospital in Mexico City. **Material and methods:** a descriptive observational study was performed, with 48 patients with vesicular polypoid lesions detected in the histopathological reports of patients undergoing cholecystectomy between January 2015 and December 2019. **Results:** 13 patients were diagnosed with true polyps (27.1%) and 35 (72.9%) with pseudo polyps. The presence of type 2 diabetes mellitus (DM2) conferred an association with an OR = 2.349 (95% CI 1.042-5.294, p = 0.038), as well as overweight, with an OR = 5.727 (95% CI 1.457-22.512, p = 0.019) for the presence of a true polyp. **Conclusions:** type 2 diabetes and being overweight confer a higher risk of a polypoid lesion being a true polyp; these factors should be considered for management decisions since true polyps confer malignant potential.

RESUMEN

Introducción: *los pseudopólipos de vesícula biliar se consideran lesiones benignas, mientras que los pólipos verdaderos se relacionan con la secuencia adenoma-adenocarcinoma de vesícula biliar.* ***Objetivo:*** *determinar si existen factores de riesgo sociodemográficos o clínicos relacionados con la presencia de pólipos vesiculares verdaderos en pacientes con lesiones polipoides sometidos a colecistectomía en un Hospital del Tercer Nivel de la Ciudad de México.* ***Material y métodos:*** *se realizó un estudio observacional descriptivo, con un total de 48 pacientes con lesiones polipoides vesiculares detectadas en los reportes histopatológicos de pacientes sometidos a colecistectomía en el periodo comprendido entre enero de 2015 y diciembre de 2019.* ***Resultados:*** *13 pacientes contaron con diagnóstico de pólipo verdadero (27.1%) y 35 (72.9%) de pseudopólipo. La presencia de diabetes mellitus tipo 2 (DM2) confirió una asociación con OR = 2.349 (IC 95% 1.042-5.294, p = 0.038), así como sobrepeso, con un OR = 5.727 (IC 95% 1.457-22.512, p = 0.019) para la presencia de pólipo verdadero.* ***Conclusiones:*** *la presencia de diabetes tipo 2 y sobrepeso confiere un riesgo mayor de que la lesión polipoide sea un pólipo verdadero; se deben tener en cuenta estos factores para la toma de decisiones en su manejo, ya que los pólipos verdaderos confieren potencial maligno.*

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INTRODUCTION

Vesicular polyps are elevations in the gallbladder mucosa that project into the lumen.[1] These polypoid lesions are found in 4-6% of healthy adults.[2] In some series, a prevalence of up to 9.5% has been found.[3] They are usually asymptomatic, and most are detected incidentally by an abdominal ultrasound performed for another cause or when performing the histopathological study after cholecystectomy.[2,4] Their incidence is increasing due to the increased use of abdominal imaging techniques,[4] reaching a prevalence of 7% of all abdominal ultrasounds.[5]

Vesicular polyps are classified into pseudo polyps and true polyps. Pseudo polyps can be adenomyomas, inflammatory or hyperplastic polyps, and benign lesions.[4] True polyps are further classified as benign (adenomas), premalignant (dysplastic polyps), and malignant (adenocarcinoma).[5] On ultrasound, a polyp is seen as an elevation of the gallbladder wall protruding into the lumen.[1] In terms of prevalence, pseudo polyps are more common than true polyps.[6,7]

Benign gallbladder disease usually presents with localized intraluminal lesions, which include lithos, cholesterol polyps, and adenomas. Polyp size, wall thickness, and contrast uptake can differentiate cholesterol polyps from gallbladder cancer.[8] Evidence suggests that some malignant gallbladder neoplasms originate from preexisting adenomas.[9] Gallbladder adenocarcinoma is rare, and its incidence varies among ethnic groups: in Caucasians, it is 1.5/100,000, while in high-risk groups such as the Indian or Indian population, it rises to 27/100,000.[10] When the adenocarcinoma is in stage III, the five-year survival is 25%, while for stage I the five-year survival is 100%.[11] Early-stage gallbladder adenocarcinoma could be detected as a polyp by imaging studies. Some series have shown that the prevalence of malignancy in gallbladder polyps is up to 27%.[12] Since gallbladder polyps are common, but gallbladder cancer is rare, it is a diagnostic challenge to determine which polyps are likely to undergo malignant transformation and require cholecystectomy.[6]

Physicians' leading problem is more homogeneity in decision-making about which approach to take when identifying a gallbladder polyp.[13] In 2016, a consensus was reached among various international medical societies, where it was concluded that in the case of finding multiple polyps, a giant polyp would be used to decide on management. An algorithm was created that indicated performing cholecystectomy for polyps 10 mm or larger.[6] A study by Bhatt et al. identified that the probability of malignancy is about the size of the polyp. Polyps with diameters smaller than 4.15 mm have a 0% risk of malignancy, so that they may be followed up ultrasonographically.[14] They also observed other risk factors for malignancy that include: the presence of a single polyp (malignancy risk of 4.3%), presence of a sessile polyp (13.9% malignancy risk), patient age > 50 years (20.7% malignancy risk) and a single sessile polyp (24.8% malignancy risk)[14] According to Wiles and his team, risk factors for malignancy are: age > 50 years, primary sclerosing cholangitis (PSC), Indian ethnicity or the presence of sessile polyps.[6] Cha and colleagues observed that age > 65 years, diabetes, and a polyp larger than 15 mm are predictive variables for malignancy with odds ratios of 2.27, 2.64, and 4.94, respectively.[15]

The American Association for the Study of Liver Diseases recommends cholecystectomy for patients with PSC presenting a polypoid lesion.[16,17] Another risk factor is the thickening of the gallbladder wall; Zhu and collaborators observed that a wall larger than 4 mm is an independent variable for cancer.[18] In patients with gallbladder polyps between 6 and 9 mm in size without risk factors for gallbladder cancer, ultrasonographic follow-up is recommended at six months, one year, and five years. Patients who do not present risk factors and have polypoid lesions smaller than 5 mm can be managed with a more spaced follow-up, and a polypoid lesion larger than 2 mm is an indication for surgery.[6,19] Kwon and his team conducted a study with 291 cases of vesicular polyps. They found that the group with cancerous lesions had single lesions (65.7 versus 44.1%), advanced age, and sessile polyps and were accompanied by symptoms (69.2 versus 28.9%).[20]

The main objective of this study was to determine if there are sociodemographic or clinical risk factors related to the presence of true vesicular polyps in patients with polypoid lesions who underwent cholecystectomy in a tertiary-level hospital in Mexico City. The secondary objectives were to evaluate the prevalence of adenomatous (true) polyps among patients with polypoid lesions and compare preoperative ultrasonographic findings with anatomopathological findings in patients with polypoid lesions undergoing cholecystectomy.

MATERIAL AND METHODS

A descriptive observational study identified 53 patients with vesicular polypoid lesions detected in the histopathological reports of patients undergoing cholecystectomy between January 2015 and December 2019 at Hospital Médica Sur. A review of clinical records was performed, looking for sociodemographic, clinical, laboratory, and pre-surgical ultrasound characteristics. Five patients were eliminated by applying exclusion criteria, one for being younger than 18 years old and the rest for having incomplete records, obtaining 48 patients for analysis. The patients were categorized into two groups according to the presence of a true polyp or pseudo polyp. True polyps included pyloric and tubular adenomas, while pseudo polyps included cholesterol polyps and adenomyomas. The histological type of the polyp (true or pseudo polyp) was the dependent variable. SPSS (Statistical Package for the Social Sciences) v. 25.0 software was used for statistical analysis. Student's t was used for numerical variables, and only one variable was the nonparametric Mann-Whitney U test (direct bilirubin). Pearson's χ^2 was calculated with a Yates continuity correction as it was a 2×2 table; Fisher's exact test was used for having a frequency less than 5 in the cross-tables. A concordance analysis was performed using a kappa index to compare variables. All data were represented as proportions in percentages and measures of dispersion with SD (standard deviation). All values with a $p < 0.05$ were considered significant. This protocol was approved by the Hospital Médica Sur Ethics Committee and carried out per the General Health Law on Health Research provisions.

RESULTS

Population: demographic and clinical characteristics are listed in *Tables 1 and 2*. The mean age was 47.78 years (± 16.53). Thirty-five patients (72.9%) were female, and 13 (27.1%) were male. The mean height was 1.63 m (± 0.87), and the mean weight was 69.44 (± 12.52). A mean body mass index (BMI) of 25.66 (± 5.34) was identified. Nineteen patients were identified as overweight (39.6%) and seven as obese (14.6%). Regarding comorbidities, 18 patients (37.5%) had a history of smoking, eight (16.7%) with systemic arterial hypertension, six (12.5%) with diabetes mellitus (DM), and 22 patients (45.8%) showed a risk factor related to gallbladder cancer. Of the patients, 14.6% showed preoperative symptomatology, such as right hypochondrium pain. Preoperative liver function tests were analyzed, finding a mean total bilirubin of 1.28 (± 2.4), mean direct bilirubin of 0.59 (± 2.09), and indirect bilirubin of 0.69 (± 0.5). By ultrasound findings, seven patients (14.6%) had thickening of the gallbladder wall, and 25 (52.1%) had gallbladder lithiasis. In 25 patients (52.1%), there was the detection of polypoid lesions, of which 12 (25%) had a polyp of 6-9 mm and 13 (27.1%) had a polyp smaller than 6 mm. In 11 patients (22.9%), multiple polyps were detected.

Histopathological analysis: thickening of the gallbladder wall was detected in eight patients (16.7%), gallbladder lithiasis in 17 (35.4%), and the presence of cholesterosis in 21 (43.8%). There were 25 patients (52.1%) with multiple polyps and 23 with single polyps (47.9%). In the total sample (48 patients), the diagnosis of polypoid lesion was confirmed by histopathological analysis; of these, 13 corresponded to a true polyp (27.1%) and 35 (72.9%) to a pseudo polyp.

Comparison of true polyps versus pseudo polyps: gender, BMI, age, obesity, hypertension, smoking, and symptoms showed no difference between the two groups *(Table 3)*. The presence of DM2 conferred an association with an OR = 2.349 (95% CI 1.042-5.294, p = 0.038) and

Table 1: Numerical variables represented by mean and standard deviation as measures of dispersion. N = 48.

Numerical variables	
Age	47.7885 ± 16.53794
Height	1.6322 ± 0.08764
Weight	69.44 ± 12.52
Body mass index	25.6605 ± 5.34660
Total bilirubin	1.2808 ± 2.48852
Direct bilirubin	0.5906 ± 2.09544
Indirect bilirubin	0.6946 ± 0.50272
Aspartate aminotransferase	41.1000 ± 70.27232
Alanine aminotransferase	57.9700 ± 181.29430
AP	80.7542 ± 73.30147
Gamma-glutamyl transferase	55.44 ± 144.58
Lactate dehydrogenase	154.76 ± 48.734

AP = alkaline phosphatase.

Table 2: Qualitative variables. Frequencies and proportions. N = 48.

Qualitative variables	n (%)
Female gender	35 (72.9)
Overweight	19 (39.6)
Obesity	7 (14.6)
Type 2 diabetes	6 (12.5)
Hypertension	8 (16.7)
Smoking	18 (37.5)
Presence of symptoms	7 (14.6)
Presence of cancer risk factors	22 (45.8)
Ultrasound parameters	
Wall thickening	7 (14.6)
Vesicular lithiasis	25 (52.1)
Presence of polypoid lesion	25 (52.1)
Polyps 6-9 mm	12 (25.0)
Polyps < 6 mm	13 (27.1)
Multiple polyps	11 (22.9)
Pathology parameters	
Wall thickening	8 (16.7)
Vesicular lithiasis	17 (35.4)
Multiple polyps	25 (52.1)
Single polyp	23 (47.9)
True polyp	13 (27.1)
Pseudo polyp	35 (72.9)
Cholesterolosis	21 (43.8)

overweight with an OR = 5.727 (95% CI 1.457-22.512, p= 0.019) for the presence of a true polyp. No significant difference was observed between the two groups in any parameter of the liver function tests or ultrasound *(Tables 4 and 5)*. When comparing the pre-surgical ultrasound variables with the pathology report, concordance was only observed with the presence of gallstones, with a Kappa index of 0.43 (p = 0.0015) *(Table 6)*.

DISCUSSION

Gallbladder polyps are common lesions; an incidence of these lesions has been reported from 0.3 to 12% of the population. They should not be overlooked because of their association with the development of gallbladder cancer.[15] A higher frequency of gallbladder polyps has been observed in women than men. In agreement with this, of the polyps detected in our study, it was observed that most cases corresponded to women (72.9%).[21] The presence of polyps increases with age and tends to be detected more frequently in patients between 40 and 50. In our sample, the mean age was within this range.[3] Several studies have shown the association between different risk factors and the presence of vesicular polyps. Among the known risk factors, the following stand out: female gender, overweight, obesity, and metabolic syndrome. Our study observed a prevalence of 39.6% for overweight, 14.6% for obesity, and 12.5% for type 2 diabetes (T2D).[22] The study of choice for diagnosing vesicular polypoid lesions is ultrasound. A meta-analysis performed by Cochrane, which included 16 clinical studies, identified that the sensitivity and specificity of transabdominal ultrasound for the detection of polyps is 0.84 (95% CI 0.59-0.95) and 0.96 (95% CI 0.92-0.98), respectively. In our study, preoperative ultrasound only detected vesicular polypoid lesions in 52.08% of cases (25/48).[23,24]

Vesicular polyps are classified into pseudo polyps and true polyps. The former corresponds to cholesterol polyps, adenomatous polyps, or adenomyomas, considered benign lesions. True polyps correspond to adenomas associated with the risk of malignant progression. In a study by Sarkut et al., 99 cases of vesicular polyps were detected by histopathological study, of which

77 (77.7%) corresponded to pseudopolyps and 22 to true polyps. In our study group, of the 48 cases of polypoid lesions, 35 (72.9%) corresponded to pseudopolyps.[4] True polyps are known to be related to the adenoma-adenocarcinoma sequence for gallbladder cancer.[8] Although there is still controversy in the management of polypoid lesions, guidelines have been created to standardize their management, which is based on the size of the polyp and the presence of risk factors for cancer.[6] The guidelines recommend cholecystectomy for 10 mm or more significant polyps and ultrasonographic follow-up for those smaller than 6 mm. For polyps between 10 and 6 mm in size, surgery is recommended when the following risk factors for gallbladder cancer are present: age over 50 years, history of primary sclerosing cholangitis, Indian or Chilean population, and the presence of sessile polyps. In our study, 22 patients (45.8%) had only one risk factor, corresponding to age over 50; we did not detect patients with the other risk factors mentioned.[6] When dividing the study population into those with true gallbladder polyps and those with pseudo polyps, we found no statistical difference in the following variables: gender, BMI, age, obesity, smoking, clinical, nor in the variables of liver function tests or preoperative ultrasound. Only overweight (BMI 25-29.9 kg/m^2) and T2D were related to the presence of true polyps with a significant difference.

In a retrospective observational study conducted by Lee et al., it was observed that T2D is an independent risk factor related to the development of true vesicular polyps with a statistically significant measure of association (OR 2.942, 95% CI 1.061 to 8.158, p = 0.038), which supports our results.[25] Our study proves the association of being overweight with the development of true vesicular polyps, a precursor lesion of malignant neoplasia.[9] Adipose tissue is a highly dynamic endocrine organ that constitutes a central piece in the adiponectin network, which causes pleiotropic effects in the organism, including inflammation. In addition, neoplasms of the gastrointestinal tract grow anatomically close to adipose tissue.[26] These findings support the importance of detecting risk factors associated with developing true gallbladder polyps, representing the pathological basis for developing gallbladder cancer. Being overweight and having T2D

Table 3: Statistical analysis of categorical and numerical variables and their association with the development of true polyps.

Polyp vs. pseudo polyp	p	OR (95% CI)
Gender	0.300	0.364 (0.70-1.888)
Type 2 diabetes	0.038	2.349 (1.042-5.294)
Body mass index	0.140	Not applicable
Age	0.286	Not applicable
Obesity	0.662	0.381 (0.42-3.431)
Overweight	0.019	5.727 (1.457-22.512)
Hypertension	0.674	1.650 (0.348-7.821)
Smoking	0.618	1.714 (0.478-6.151)
Compatible clinical manifestations	0.420	0.435 (0.100-1.888)

OR = *odds ratio*. 95% CI = 95% confidence interval.

Table 4: Analysis of laboratory values between polyps and pseudopolyps.

	Levene's test for variance equality				
Variable	**F**	**Sig.**	**t**	**GL**	**p**
Total bilirubin	8.757	0.005	1.489	50	0.143
			0.882	12.276	0.395
Indirect bilirubin	1.288	0.262	1.219	50	0.229
	–	–	0.920	14.494	0.373
Aspartate aminotransferase	0.051	0.823	0.070	50	0.944
	–	–	0.095	41.227	0.925
Alanine aminotransferase	0.506	0.480	-0.327	50	0.745
	–	–	-0.530	47.867	0.599
Alkaline phosphatase	0.131	0.719	-0.121	50	0.904
	–	–	-0.114	18.779	0.911
Gamma glutamyl-transpeptidase	2.963	0.091	0.979	50	0.332
	–	–	0.710	14.012	0.489
Lactate dehydrogenase	0.049	0.826	-0.762	37	0.451
	–	–	-0.921	14.746	0.372
	U-value				
Direct bilirubin	-0.625*				0.532

* U value = to nonparametric Mann-Whitney U test.

Table 5: Association of ultrasound features with the finding of true polyps.

True polyp vs. pseudo polyp	Value	Degrees of freedom	p	OR
Thickened wall	–	1	0.203	3.022 (0.670-13.628)
Multiple polyps	–	1	0.703	1.833 (0.340-9.886)
Polypoid lesion	0.103	1	0.749	0.814 (0.231-2.866)
Lithiasis	–	1	0.523	1.867 (0.518-6.731)

OR = *odds ratio.*

as risk factors associated with developing true gallbladder polyps is a finding consistent with previous retrospective observational studies. According to Ali and colleagues, the prevalence of gallbladder polyps is significantly higher in patients with overweight, T2D, and hypertension.[27] Although hypertension was not statistically significant in our sample, there is biological plausibility to suggest that the metabolic syndrome represents a risk for the development of true gallbladder polyps. Regarding ultrasound as a diagnostic method, we found that there is a significant concordance of ultrasound for the detection of gallbladder stones, with a K-index = 0.43, with a significant p value, but not for the detection of polypoid lesions, wall thickening, or multiple polyps.

Table 6: Analysis of concordance by Kappa index for comparison of histopathology results and gallbladder and biliary tract ultrasound.

Pathology vs. ultrasound concordance analysis	Kappa	p
Presence of polypoid lesions	-0.061	0.612
Wall thickening	-0.026	0.512
Presence of multiple polyps	0.097	0.394
Presence of vesicular lithiasis	0.432	0.0015

CONCLUSIONS

This study demonstrates that the presence of T2D and overweight confer a higher risk of the polypoid lesion being a true polyp, with an odds ratio of 2.34 and 5.72, respectively. These factors should be considered when making management decisions because as they are more associated with true polyps, there is a greater risk of malignant potential. One of the study's secondary objectives was to identify true vesicular polyps (adenomas) prevalence. Our study found a prevalence of 27.08% of these lesions within the total of vesicular polypoid lesions. There are few studies on vesicular polyps in the Mexican population, and of these, most of them analyze their frequency and associations based on polyps detected by ultrasonography.

Our study performed a retrospective analysis based on cases detected by pathology (gold standard) and observed that ultrasound is unreliable for detecting these polyps. Among the limitations of our research, we found that it is a retrospective study, so it does not allow us to determine the incidence of the disease. Another limitation is that it involves a moderate number of patients and is limited to a single center, so similar investigations with larger and multicenter samples will be required to confirm the associations we detected.

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Ethical considerations: all procedures were performed by the stipulations of the Regulations of the General Health Law on Health Research. The protocol did not confer risk for the study population because it was a retrospective and descriptive study. By agreement of the Hospital Médica Sur, all the information from the medical records was previously authorized by the patients, who, upon admission, signed permission to use their records (always protecting their confidentiality) for academic and research purposes (non-experimental studies). The confidentiality of the data was ensured through the description of results with identification by file number or clinical characteristics and never by the name or personal data of any patient.

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