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THE RELATIONSHIP BETWEEN TYPE 2 DIABETES MELLITUS AND GALLSTONES: A CROSS-SECTIONAL STUDY

[1]*Sobhi Alliwa, [2]Arige Boubou and [3]Hassan Zayzafon

[1]Department of Endocrinology, Master of Endocrinology at Faculty of Medicine, Tishreen University, Lattakia, Syria.
[2]Department of Endocrinology, Instructor of Endocrinology at Faculty of Medicine, Tishreen University, Lattakia, Syria.
[3]Department of Gastroenterology, Professor of Gastroenterology at Faculty of Medicine, Tishreen University, Lattakia, Syria.

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***Corresponding Author: Dr. Sobhi Alliwa**

Department of Endocrinology, Master of Endocrinology at Faculty of Medicine, Tishreen University, Lattakia, Syria.

ABSTRACT

Background: Diabetes and gallstones are among the most common and costly diseases. Several studies found an increased prevalence of gallstones in diabetics, but with a high variation in percentages. The results of these studies were also inconsistent concerning potential risk factors for gallstone formation in type 2 diabetes mellitus (T2DM) patients, such as age, gender, and obesity. **Aim of the study:** This study aimed to assess the prevalence of Gallstones in T2DM patients and the associated risk factors such as age, gender, duration of diabetes, HbA1c level, parity, family history of gallstones, obesity, and dyslipidemia. **Materials & Methods**: A cross-sectional study included 243 T2DM patients who attended Tishreen University Hospital from 1st February 2020 to 1st September 2021. We performed a comprehensive clinical examination, measurement of height and weight. Venous blood samples were drawn after a 12-hour fast: ALT, AST, triglycerides, total cholesterol, HDL, HbA1c, TSH, blood sugar, CBC, Creatinine. An abdominal ultrasound was also performed after A 8 hours fast to look for gallstones or Biliary sludge. **Results:** The prevalence of gallstones in T2DM patients was 25.5%. Advanced age, increased duration of diabetes, obesity, multiple parity, family history of gallstones, high total cholesterol and triglyceride levels, as well as low levels of HDL were associated with a high risk of gallstones in patients with type 2 diabetes. The gallstones prevalence was 29% in women and 20.4% in men, but this difference was not statistically significant. A high level of HbA1c was not a risk factor for gallstone formation. **Conclusion:** Patients with type 2 diabetes have a higher prevalence of Gallstones than non-diabetics.

KEYWORDS: Type 2 diabetes mellitus, gallstones, ultrasound imaging, diabetes complications.

INTRODUCTION

The number of diabetes mellitus (DM) patients in the age group between (20-79 years) have steadily increased from 151 million in 2003 to 463 million in 2019, and this number is expected to reach 700 million in 2045.[1] The International Diabetes Federation estimates that diabetes-related health expenditures in 2014 amounted to 11% of total health expenditures on adults. The Centers for Disease Control and Prevention (CDC) reports that the costs of diabetes in the United States were $245 billion, and per capita, spending is 2.3 times higher than that of people without DM.[2]

Cholelithiasis is a major cause of morbidity in the United States and Europe. The prevalence of asymptomatic gallstones is 10-15% in the European population,[3] while symptomatic gallstones are less frequent; 2% of the population.[4] Gallstones are the most common and costly disease of the digestive system that requires hospitalization. The economic costs of treating gallstones in hospitals exceed 6.5 billion US dollars.[5]

The results of epidemiological studies on the risk of developing gallstones in patients with DM were conflicting, as some studies found an association between DM and the risk of developing gallstones,[6,7,8] while other studies did not find any association.[9,10,11] In

addition, the level of risk varied widely, which may be due to confusion with other risk factors.

Data on the prevalence of gallstones in patients with type 2 diabetes mellitus (T2DM) and associated risk factors are scarce in our country. Given that we expect that the prevalence of diabetes would rise dramatically over the next two decades, it will be important to clarify whether there is an association between DM and the risk of developing gallstones. In addition, defining the risk factors of gallstones in T2DM patients will prompt us to investigate the presence of gallstones early, even in the absence of typical symptoms. That will avoid the important complications and reduce the high financial cost.

MATERIALS AND METHODS

We carried out this study to assess the prevalence of gallstones in adult men and women with T2DM. Besides, we wanted to study the potential risk factors for gallstones formation, such as age, gender, duration of diabetes, hemoglobin level, Parity, a family history of gallstones, obesity, and dyslipidemia. A cross-sectional study included 243 T2DM patients who attended Tishreen University Hospital from 1st February 2020 to 1st September 2021. Exclusion criteria were: patient age <30 years, T2DM duration <1 year, patients with chronic liver disease, celiac disease, Crohn's disease, gastrectomy, sickle cell anemia, hemolytic anemia, hypothyroidism, pregnant women, women using oral contraceptives and replacement hormone therapy, and patients currently treated with Clofibrate and Ceftriaxone.

Patients provided written informed consent to participate in the study. We performed a comprehensive clinical examination and calculated the body mass index (BMI). Besides, we drew venous blood samples after a 12-hour fast and assayed: ALT, AST, triglycerides, total cholesterol, HDL, HbA1c, TSH, hypoglycemia, CBC, Creatinine. We performed abdominal ultrasonography after A 8 hour fast to look for gallstones or Biliary sludge.

Definitions

Studied variables included gender, age, BMI, diabetes duration, HbA1c, parity, family history of gallstones, total cholesterol, High-density lipoprotein (HDL), triglycerides. The outcome was defined as gallstones, positive or negative. Gallstones positivity is defined by the presence of gallstones that are seen by abdominal ultrasonography and/or bile sludge or excised gallbladder caused by gallstones that diagnosed after 1 year at least of T2DM diagnosis.

STATISTICAL ANALYSIS

Descriptive Statistics: We used frequencies and percentages for qualitative variables and measures of central tendency for quantitative variables.

Inferential Statistics: We used the Chi-square test to study the relationship between qualitative variables and Student's t-test to determine if the means of two sets of data are significantly different from each other. Results were statistically significant when p-value <0.05. The program (IBM SPSS statistics) version19 was adopted to calculate statistical transactions and analyze results.

RESULTS

Our study sample included 243 T2DM patients whose ages ranged between 35-80 years. We clarify the research sample distribution according to the studied variables in (Table 1).

Table 1: Distribution of the sample according to the studied variables.

Variables	Number of patients	(%)
Gender:		
Male	98	(40.3)
Female	145	(59.7)
Age: (year)		
30-39	19	(7.8)
40-59	117	(48.1)
60-80	107	(44)
DM duration (year)		
1-<5	89	(36.6)
5-10	72	(29.6)
>10	82	(33.7)
BMI: (kg\m^2)		
<18.5	0	(0)
18.5-24.9	92	(37.9)
25-29.9	78	(32.1)
≥30	73	(30)
HbA1c: (%)		
<7	46	(18.9)
7-9	136	(56)
>9	61	(25.1)
Parity:		
≤3	22	(15.2)
>3	123	(84.8)
Family history of gallstones		
Negative	166	(68.3)
Positive	77	(31.7)
Total Cholesterol: (mg\dl)		
≤200	112	(46.1)
>200	131	(53.9)
HDL: (mg\dl)		
≤40 male and ≤50 female	132	(54.3)
>40 male and >50 female	111	(45.7)
Triglycerides: (mg\dl)		
≤160	62	(25.5)
>160	181	(74.5)

Abbreviations. DM: diabetes mellitus; BMI: body mass index; HDL: High-density lipoprotein

The prevalence of gallstones in T2DM patients was 25.5% (62 patients). Besides, 20.4% of men and 29% of women had gallstones. When we compared the positive

gallstones group and the negative gallstones group in terms of gender, we didn't find statistical significance, but 67.74% of patients in the positive gallstones group were female. The comparison between the two groups (positive gallstones, negative gallstones) according to age yielded statistical significance concerning age mean (p=0.002), but without any significance according to age categories, although more than half of the patients with gallstones were in the age group over 60 years. When we compared the two groups according to diabetes duration, we observed that the mean of diabetes duration in patients who had gallstones was significantly greater than patients who didn't have gallstones (p=0.013). Furthermore, we found statistical significance, when we compared the two groups according to diabetes duration categories (p=0.011). (Table 1, Table 2)

The BMI mean of the positive gallstones group was greater than the negative gallstones group with a statistically significant difference (p=0.001). The highest percentage of gallstones positivity was significantly at BMI ≥30 kg/m^2 (p=0.001). We didn't find a statistically significant difference in terms of HbA1c mean, and HbA1c categories, so HbA1c is an independent variable. By comparison between the two groups, in the positive gallstones group, we found that the mean of pregnancies' number of T2DM women was more than those in the negative gallstones group with a statistically significant difference (p=0.001). In addition, 97.62% of women in the positive gallstones group had pregnancies' number >3 with statistical significance (p=0.006). We observed that 45.16% of patients in the positive gallstones group had a positive family history of gallstones, while only 27% of patients in the negative gallstones group had a positive family history of gallstones (p=0.008). (Table 1, Table 2)

The mean of total cholesterol was 203.76±32.3 mg\dl in the positive gallstones group, versus 220.02±32.66 mg\dl in the negative gallstones group (p=0.001). Furthermore, 72.58% of patients with gallstones positivity had a total cholesterol >200 mg/dl, while 27.42% of this group had total cholesterol ≤200 mg/dl (p=0.001). There was a statistically significant difference between the two groups of patients distributed according to HDL, as we found that most patients with positive gallstones had low HDL values (p=0.001). When we compared the two groups according to triglycerides, we found that patients in the positive gallstones group had a mean of triglyceride greater than those in the negative gallstones group with a statistically significant difference (p=0.001). Moreover, we detected that 93.55% of patients in the positive gallstones group had triglycerides levels >160 mg\dl. Otherwise, 6.45% of patients in the positive gallstones group had triglycerides ≤160 mg\dl (p=0.001). (Table 1, Table 2).

Table 2: Risk factors (classes) associated with the gallstone formation (univariate analysis).

Variables	Negative Gallstones N: 181	Positive Gallstones N: 62	X^2-test	P-value
Gender				
Male	78 (43.09%)	20 (32.26%)	2,253	0.133
Female	103 (56.91%)	42 (67.74%)		
Age: (year)				
30-39	17 (9.39%)	2 (3.23%)	3.486	0.175
40-59	89 (49.17%)	28 (45.16%)		
60-80	75 (41.44%)	32 (51.61%)		
DM duration (year)				
1-<5	76 (41.99%)	13 (20.97%)	8.955	**0.011**
5-10	48 (26.52%)	24 (38.71%)		
>10	57 (31.49%)	25 (40.32%)		
BMI: (kg\m^2)				
<18.5	0 (0)	0 (0)		
18.5-24.9	82 (45.30%)	10 (16.13%)	17,191	**0.001**
25-29.9	53 (29.28%)	25 (40.32%)		
≥30	46 (25.42%)	27 (43.55%)		
HbA1c: (%)				
<7	32 (17.68%)	14 (22.58%)	0,884	0,643
7-9	104 (57.46%)	32 (51.61%)		
>9	45 (24.86%)	16 (25.81%)		
Family history of gallstones:				
Negative	132 (72.93%)	34 (54.84%)	6,981	**0,008**
Positive	49 (27.07%)	28 (45.16%)		
Total Cholesterol: (mg\dl)				
≤200	95 (52.49%)	17 (27.42%)	11,678	**0,001**
>200	86 (47.51%)	45 (72.58%)		
HDL: (mg\dl)			11,185	**0,001**

≤40 male and ≤50 female >40 male and >50 female	87 (48.07%) 94 (51.93%)	45 (72.58%) 17 (27.42%)		
Triglycerides: (mg\dl) ≤160 >160	 58 (32.04%) 123 (67.96%)	 4 (6.45%) 58 (93.55%)	15,916	**0,000**
Parity: ≤3 >3	**Negative Gallstones N: 103** 21 (20.39%) 82 (79.61%)	**Positive Gallstones N: 42** 1 (2.38%) 41 (97.62%)	7,517	**0,006**

Abbreviations. DM: diabetes mellitus; BMI: body mass index; HDL: High-density lipoprotein

Table 3: Risk factors (mean) associated with the gallstone formation (univariate analysis).

Variables	Gallstones	N	Mean	Std. Deviation	t-test	P-value
Age: (year)	Negative	181	56,26	10,020	3,173	**0,002**
	Positive	62	60,84	9,157		
DM duration (year)	Negative	181	8,1561	5,36490	2,508	**0,013**
	Positive	62	10,1653	5,66788		
BMI: (kg\m2)	Negative	181	26,697	4,4928	4,874	**0,000**
	Positive	62	29,939	4,5970		
HbA1c: (%)	Negative	181	8,141	1,2122	0,277	0,782
	Positive	62	8,092	1,2206		
Parity:	Negative	103	5,64	2,842	3,351	**0,001**
	Positive	42	7,36	2,685		
Total Cholesterol: (mg\dl)	Negative	181	203,76	32,333	3,408	**0,001**
	Positive	62	220,02	32,664		
Triglycerides: (mg\dl)	Negative	181	188,34	42,166	4,270	**0,000**
	Positive	62	214,11	37,416		

Abbreviations. *DM: diabetes mellitus; BMI: body mass index*

DISCUSSION

In T2DM patients, we found that the prevalence of gallstones was 25.5% (62 patients). This percentage was high compared to the prevalence of gallstones in the general population, which reached 13.6% in Iraq[12] and 10-15% in Europe.[3] The gallstones prevalence diverges between studies and ranges from 17.7% to 39.75%.[13,14,15,16,17] The increased prevalence of gallstones in T2DM patients compared to healthy people is attributed to several reasons, such as gallbladder motility disorder, cholestasis, which is mainly caused by autonomic neuropathy, and cholecystokinin activity disorder occurring in the context of diabetes mellitus.

Also, we found that the increased mean of age of T2DM patients is associated with an increased prevalence of gallstones, and we determined a statistically significant difference between the mean age of patients who had gallstones (60.8 years) and those who didn't have gallstones (56.2 years). Furthermore, 32 patients (51.6%) whose ages ranged from 60 to 80 years old had gallstones. Several studies demonstrated that age was a risk factor for gallstones formation and this is consistent with our study.[13,14,15,17] On the other hand, Al-Bayati S. et al. didn't find a significant difference of age in gallstones formation.[16] Authors detected that an increase of DM duration was associated with an increased risk of gallstone formation,[15,16] within our study we also found that the duration of diabetes mellitus was more than 5 years in 79% of those with gallstones. That may be due to the longer duration of diabetes mellitus lasts, the more complications will occur, such as autonomic neuropathy and its effects on the gallbladder.

According to our study, obesity was one of the important risk factors for the formation of gallstones, where the mean of BMI of the positive gallstones group was 29.9 kg/m^2, while it was 26.6 kg/m^2 in the negative gallstones group with a significant statistical significance. That is consistent with the results of similar studies.[13,14,15,16,17] Patients with BMI ≥30 kg/m^2 had the highest percentage of gallstones positivity (43.55%). That is probably due to enhanced cholesterol synthesis and excretion in obese people. Our results did not display any relationship between HbA1c levels and the risk of gallstones formation. Otherwise, Al-Bayati S. et al. found that gallstones were higher in diabetic patients with increased HbA1c.[16] That may be because that the effects of elevated HbA1c levels can persist for years even after HbA1c values are reduced.[2] We demonstrated that 97.6% of T2DM women who had gallstones were multiparous females. So that the pregnancies' number of T2DM women was associated with a higher risk of gallstones formation. Other authors noted that the prevalence of gallstone disease was significantly related to parity.[14,16,17] This is because a variety of physiological changes occur in the biliary system during pregnancy and lead to a saturation of the bile with cholesterol. That saturation occurs as a result of

increased secretion of cholesterol by the influence of estrogen, as well as the relative excessive production of hydrophobic bile acids. Besides, progesterone also slows gallbladder emptying leading to cholestasis. 45.16% of patients with gallstones had a positive family history of gallstones compared to only 27% of those without gallstones. Wherefore, a positive family history of gallstones among first-degree relatives had an important statistical significance according to the results of our research. Furthermore, several studies detected that the positive family history of gallstones was an important risk factor for gallstones formation.[13,14,17]

Sodhi J. et al. demonstrated that the high triglyceride and cholesterol levels and the low high-density lipoprotein cholesterol levels were risk factors for gallstones formation.[17] That corresponds with our study, where T2DM patients with gallstones had a higher mean of total cholesterol levels compared to those without, also 72.58% of those with gallstones had total cholesterol levels of more than 200 mg/dl. Our study showed that 72.5% of patients with gallstones had low HDL levels compared to 48% of those without, and this difference was statistically significant. Moreover, the high triglyceride levels were associated with an increased risk of gallstones formation, as the results of our research showed that 93.55% of those with gallstones had high triglyceride values.

CONCLUSIONS

In our population of patients with T2DM, we found that the gallstones prevalence was higher in T2DM patients than in the general population. The prevalence of gallstones was significantly related to age, DM duration, obesity, parity, family history of gallstones, high levels of cholesterol and triglycerides, and low levels of HDL.

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LIST OF ABBREVIATIONS

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CBC: complete blood count; DM: diabetes mellitus; HbA1c: hemoglobin $A1_C$; HDL: high-density lipoprotein; T2DM: type 2 diabetes mellitus; TSH: thyroid-stimulating hormone.

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