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GALLSTONES AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

The link between gallstones formation and diabetes mellitus remains controversial. The study aims to find the prevalence of gallstones in diabetic patients and its relation with status of control, and duration of diabetes mellitus.

A case-control study was conducted in Al-Basrah General Hospital; Basrah city, southern Iraq from January 2015 to September 2015. The study enrolled 100 type 2 diabetic patients with no abdominal pain (60% females, 40% males) as a test group and 100 asymptomatic subjects with no diabetes mellitus (60% females, 40% males) as a control group. Both groups were comparable for gender, age, and body mass index and examined by ultrasound to find gallstones. Blood samples were taken for fasting blood glucose and body mass index was measured. Age, gender, family history of gallstones, and parity for females were recorded in both groups. The tested group was further divided into two subgroups with and without gallstones. The association between duration of diabetes mellitus and hemoglobin A1c level with gallstones was assessed.

Gallstones were detected in (28%) of diabetic group and (12%) of controls, which was highly statistically significant (p value=0.005). The prevalence of gallstones was found to be significantly higher among those with more than 10 years of diabetes and poor glycemic control compared with those with less than 5 years and good glycemic control.

The study suggested that diabetic patients are at higher risk for gallstones in comparison to non-diabetic patients. Gallstones are found to be higher in those patients with long duration of diabetes mellitus and poor glycemic control.

Introduction

Gallstones are solid substances in the gall-bladder because of changes in the composition of bile; increase cholesterol, increased amount of pigment material, decrease bile acid[1], and/or impaired gallbladder contraction, which would lead to inadequate gallbladder emptying after a fatty meal[2]. They are divided into two main types: cholesterol gallstones which account of more than 90% of the total, and pigment gallstones which are categorized into black and brown types[3].

The prevalence of cholesterol gallstone disease is rising in industrialized countries of Europe and North America[4]. The lowest prevalence is seen in Africans[5] and very low in south-east Asia[6].

Many studies from around the world reported an increased prevalence of gallstones in patients with type2 diabetes. Although the association between diabetes mellitus type2 and gallstones is controversial, many studies revealed that diabetic patients are two to three times more risky for gallstones than non-diabetics[7].

How diabetes predisposes to gallstones is not well understood. However, hypertriglyceridemia[8], inadequate emptying of gallbladder and increased volume[9], autonomic neuropathy (leading to gallbladder hypo- motility and biliary stasis)[10] and hyperinsulinemia have been suggested as contributing factors to the increased risk of gallstone development in diabetics[11].

Ultrasonography is a rapid, noninvasive method for imaging the gallbladder, which has contributed greatly to our

understanding of the epidemiology of and risk factors for gallstones[12].

The study aim was to find the prevalence of gallstones in diabetic patients, and its relation with status of control and duration of diabetes mellitus, and also with age, gender, BMI and family history of gallstones.

Patients and Methods

This case control study was conducted in Al-Basrah General Hospital, Basrah city, southern Iraq from January 2015 to September 2015. One hundred patients with type 2 diabetes mellitus were enrolled in this study (after obtaining their consent) as a test group, (60) females and (40) males, all subjects in test group were fulfilled the WHO criteria for diagnosis of diabetes mellitus. One hundred subjects with no diabetes mellitus (60 females and 40 males) were studied as a control group, samples of venous blood from antecubital fossa vein were sent for fasting or random blood sugar to rule out the possibility of undiagnosed diabetes mellitus by reading less than 7 mmol/L and less than 11.1 mmol/L for fasting or random blood sugar respectively, according to criteria of American Diabetic Association[13].

Test group patients were asked about the date of their diagnosis and duration of disease and accordingly patients were subdivided into those with duration <5 years, between 5-10 years and those with duration >10 years. Blood samples were drained from patients to determine the HbA1C level, and they were subdivided in to 3 groups; those with HbA1C<7, HbA1C 7-9.9 and HbA1C≥10.

Individuals in both groups were asked about their ages; accordingly they were subdivided into those with age (30-39) years, (40-49) years, (50-59) years, (60-69) years, and (70-79) years. Family history of gallstones was obtained and the females were asked about the number of pregnancies and subdivided into those with parity ≤3 and >3. The body mass index was calculated by dividing the weight in kilograms by square of patient's height in meters (m2) and subjects were subdivided into those with BMI <18.5 (underweight), BMI between 18.5-24.9 (normal weight), those with BMI 25-29.9(overweight) and those with BMI ≥30 (obese) .

Ultrasound was performed by trained operators unaware of subjects' history. Gallstones defined as mobile echoes in gallbladder lumen. The final gallbladder status was recorded as normal or presence of gallstones.

The study was conducted in 2 phases. In the first phase, test and control groups were compared to determine the prevalence of gallstones in both. Both groups were compared for age, gender, body mass index and family history of gallstones. The second phase was a comparison study within diabetic patients to determine the effect of duration of diabetes, and level of HbA1C on prevalence of gallstones.

Subjects excluded from the study were:

1. Those <30 years or ≥80 years.
2. Those with onset of diabetes mellitus prior to age of 30 year or treated initially by insulin or with history of diabetic ketoacidosis because they were considered as having diabetes mellitus type 1.
3. Any patient with false reading HbA1C such as:

- Hemoglobinopathy by history, clinically or available blood picture.
- Recent blood transfusion
- Patients on hemodialysis
- Anemia discovered clinically or by available blood picture.

4. Pregnancy.
5. Subjects who underwent gastrointestinal surgery.

Data obtained were analyzed using the statistical package for social sciences (SPSS) software version 20.0. Descriptive analysis was done using mean±standard deviation, frequency and percentage of

each value. P value less than 0.05 was considered significant.

Results

Forty (20%) subjects out of 200 of studied population had gallstones, 28(28%) of them were in test group, and 12(12%) in control group, the difference was statistically significant (p=0.005), Table (I).

Demographic distribution of the study; showed that the majority of subjects who participated in the study were females 60(60%) and minority were males 40(40%) in both groups. Their ages ranged between 30-79 years with a mean of (51.6±9.5) and (50.62±12.9) years in test and control groups respectively. Body mass index ranged between (<18.5->30) with a mean of (31±6.3) in test group and (26.52±6.1) in control group. 24(24%) had family history of gallstones, while 76(76%) with no family history in test group in comparable with 17(17%) had family history of gallstones, while 83(83%) with no family history in control group. The mean of the parity was (6±3.7) in test group and (5.46±3.1) in control group. The mean duration of diabetes mellitus was (10.47±5.43) year. HbA1c ranged between (<7-≥10) with a mean of (9.5±2.6), Table (II).

The prevalence of gallstones was significantly associated with an increasing age in both diabetic and non-diabetic subjects. Although there were mild differences between both groups, but statistically insignificant (P=0.3), Table (III).

The prevalence of gallstone had increased with increasing body mass index in both diabetic and non-diabetic subjects, and the difference was statistically significant (p=0.027), Table (IV).

Number of subjects with positive family history of gallstone were more than those without family history, although the difference was statistically not significant (P=0.42), Table (V).

The prevalence of gallstones had increased in diabetic females as compared to non-diabetics, and this was statistically significant differences (P=0.046), Table (VI).

The prevalence of gallstones had increased in diabetic females with increasing parity as compared to non-diabetic females (36%, 4.6% respectively). This was statistically significant differences (P=0.033), Table (VII).

The prevalence of gallstones was found to be significantly higher among those with long duration of diabetes of more than 10 years as compared with those with short duration of diabetes of less than 5 years (P=0.006) .This was statically significant, Table (VIII).

The prevalence of gallstones had increased from 11.8% in diabetic patients with HbA1C level <7 to 42.1% at HbA1C level ≥10. The difference was found to be statistically significant (P=0.01), Table (IX).

Table I: The prevalence of gallstones in test and control groups:

		Gallstone		Total
		+ve	-ve	
subjects	Test group	28(28%)	72(72%)	100
	Control group	12(12%)	88(88%)	100
Total		40	160	200

X^2 =8 df=1 P=0.005

Table II: Demographic distribution of the study groups:

Variables		Test group		Control group	
		NO. (%)	Mean ± SD	NO. (%)	Mean ± SD
Age	30-39	12(12%)	51.6±9.5	24(24%)	50.62±12.9
	40-49	30(30%)		21(21%)	
	50-59	36(36%)		27(27%)	
	60-69	19(19%)		19(19%)	
	70-79	3(3%)		9 (9%)	
Gender	Male	40(40%)		40(40%)	
	Female	60(60%)		60(60%)	
BMI	<18.5	1(1%)	31±6.3	2 (2%)	26.52 ±6.1
	18.5-4.9	13(13%)		46(46%)	
	25-29.9	33(33%)		31(31%)	
	≥30	53(53%)		21(21%)	
Family history of Gallstone	Positive	24(24%)		17 17%)	
	Negative	76(76%)		83(83%)	
Parity	≤3	10(10%)	6±3.7	17(17%)	5.46 ± 3.1
	>3	50(50%)		43(43%)	
Duration of diabetes	<5	10(10%)	10.47±5.43		
	5-10	48(48%)			
	>10	42(42%)			
HbA1C	<7	17(17%)	9.5±2.6		
	7-9.9	45(45%)			
	≥10	38(38%)			

Table III: The relation between gallstones and age in test and control groups:

Age (years)	Test group		Control group		TOTAL NO. OF GS
	Total number	With GS NO. (%)	Total number	With GS NO. (%)	
30-39	12	1(8.3%)	24	2(8.3%)	3
40-49	30	7(23.3%)	21	3(14.2%)	10
50-59	36	12(33.4%)	27	4(14.8%)	16
60-69	19	8(42.1%)	19	3(15.7%)	11
70-79	3	0(0%)	9	0(0%)	0
Total	100	28	100	12	40

X^2 =2.15 df=4 P=0.34

Table IV: The relation between gallstones and BMI in test and control groups:

BMI	Test group		Control group		TOTAL NO. OF GS
	Total number	With GS NO. (%)	Total number	With GS NO. (%)	
<18.5	1	0(0%)	2	0(0%)	0
18.5-24.9	13	2(15.3%)	46	5(10.8%)	7
25-29.9	33	10(30.3%)	31	3(9.6%)	13
≥30	53	16(30.1%)	21	4(19%)	20
Total	100	28(28%)	100	12(12%)	40

X^2= 6.970 df=3 P= 0.027

Table V: Relation between gallstones and family history in test and control groups:

Family history	Test group		Control group		Total NO. of GS
	Total number	With GS NO. (%)	Total number	With GS NO. (%)	
Positive	24	8(33.3%)	17	5(29.4%)	13
Negative	76	20(26.3%)	83	7(8.4%)	27
Total	100	28	100	12	40

X^2= 0.657 df=1 P = 0.42

Table VI: The relation between gallstone and gender in test and control groups:

Gender	Test group		Control group		Total NO. of GS
	Total number	With GS NO. (%)	Total number	With GS NO. (%)	
Male	40	7(17.5%)	40	7(17.5%)	14
Female	60	21(35%)	60	5(8.3%)	26
Total	100	28	100	12	40

X^2= 4.103 df=1 P= 0.046

Table VII: The relation between gallstone and parity in test and control groups:

Parity	Test group		Control group		Total No. of GS
	Total number	With GS NO. (%)	Total number	With GS NO. (%)	
≤3	10	3(30%)	17	3(17.6%)	6
>3	50	18(36%)	43	2(4.6%)	20
Total	60	21	60	5	26

X^2= 4.754 df=1 P= 0.033

Table VIII: The relation between the duration of diabetes mellitus and gallstones in diabetic patients:

Duration of diabetes (year)	Total number	Diabetic with GS NO. (%)	Diabetic without GS NO. (%)
<5	10	1(10%)	9(90%)
5-10	48	9(18.75%)	39(81.25%)
>10	42	18(42.9%)	24(57.1%)
Total	100	28	72

X^2= 8.243 df=2 P=0.006

Table IX: The relation between HbA1c nd gallstones in diabetic patients:

HbA1C	Total number	Diabetic with GS NO. (%)	Diabetic without GS NO. (%)
<7	17	2(11.8%)	15(88.2%)
7-9.9	45	10(22.2%)	35(77.8%)
≥10	38	16(42.1%)	22(57.9%)
Total	100	28	72

X^2= 6.718 df=2 P = 0.01

Discussion

Gallstone disease is one of the most common digestive diseases[5], and can occur anywhere within the biliary tree, including the gallbladder and the common bile duct[14]. Several studies from across the world reported an increased prevalence of gallstones in patients with diabetes mellitus[10].

This study has shown; that the frequency of gallstones is more in diabetic patients (28%) as compared with those non-diabetics (12%). These results were similar to previous study that was done by AL-Bayati et al[15] who showed that there was a higher prevalence of gallstone in diabetics (33%) as compared to controls (17%). Also Elmehdawi R et al[16], showed that(39.75%) of Type 2 diabetes mellitus patients have ultrasonographic evidence of gallstones as compared to (17.5%) of healthy subjects.

Although age and family history of gallstones are well-recognized risk factors for the gallstones in both diabetics and non-diabetics but this study showed no statistically significant differences between the age, family history of gallstones and diabetes mellitus. This was similar to previous results of studies[17-21]. This can be explained by that increasing age causes increased biliary secretion of cholesterol, decreased size of bile acid pool, decreased secretion of bile salts[3].

Obesity and overweight are well-known risk factors for the development of gallstones, this study has shown that the gallstones were more prevalent in overweight diabetics than in non-diabetics (30.1%, 19% respectively). These results agree with a study done by A. B. Olokoba et al[22], who found that diabetic patients had a significantly higher body mass index than the controls ($P < 0.01$) in 100 type 2 diabetic patients and 100 age- and sex-matched controls. However, obesity alone is independent risk factor among obese type 2 diabetic patients and a number of other factors are responsible for the increasing incidence of gallstones in type 2 diabetes mellitus. In diabetics, lipid concentration of plasma and bile are increased, and obesity observed in diabetic patients has diverse effects on increased cholesterol synthesis, secretion, and bile saturation[23].

Diabetic women were more affected than non-diabetics women (35%, 8.3% respectively). The results of the study are in harmony with the results of Sodhi JS et al[24]. The higher rate in women is probably due to the effects of sex hormones and pregnancy. Estrogen causes an increase in cholesterol secretion while progesterone causes reduction in bile acid secretion[25]. These changes eventually lead to super saturation of bile with cholesterol, which facilitates gallstones formation. Oral contraceptive pills which contain more than 50 microgram of estrogen dose, are also contributing factor[26].

The number of parity in diabetic women with gallstones was significantly higher than those of non-diabetics with gallstone (36%, 4.6% respectively). These results were similar to study done by Chapman BA et al[19]. This association could be due to qualitative changes in bile and slowing of gallbladder emptying, which promotes bile stasis during multiple pregnancies[17,19].

The duration of diabetes was positively related to the prevalence of gallstone. These results agree with a study done by AL-Bayati et al[15]. However, another previous studies didn't show such an association[27,28]. This association could be the result of increased insulin resistance and increased risk of autonomic neuropathy with longer duration of diabetes mellitus[29].

There was a significant relationship between gallstones and increased hemoglobin A1C level which indicate a poor glycemic control[3]. This result was in agreement with a previously published study done by MacGregor IL et al[28], which showed that gallstone formation was significantly greater in diabetics with high HbA1c level. Since the level of blood

glucose concentration affect gallbladder motility in a way that an acute hyperglycemia reduces the gallbladder responsiveness to cholecystokinin-33 (CCK-33) in a dose dependent manner and that hyperglycemia reduces basal and CCK-33 stimulated plasma pancreatic polypeptide (PP) concentration, suggesting impaired cholinergic activity during hyperglycemia[28].

This study has concluded that the prevalence of gallstones was more in patients with diabetes mellitus especially in those with long duration of diabetes mellitus and those with poor glycemic control as compared to non-diabetic patients.

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