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Prevalence of Gall Bladder Stones among Type 2 Diabetic Patients in Benghazi Libya: A Case-control Study

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Abstract:

Background: Diabetes mellitus and gall bladder stones are both common and costly diseases. Increasing age, female gender, overweight, familial history of the disease and type 2 diabetes mellitus is all associated with an increased risk of gallstones. Several studies from around the world reported an increased prevalence of gall bladder stones in patients with diabetes mellitus. **Aims and objectives:** The aim of this study was to define the frequency of gall bladder stones among Libyan diabetics and to evaluate the possible associated risk factors in these patients. **Patients and methods:** A case-control study was performed during 2007 at Benghazi Diabetes and endocrinology Center. The study involved 161 randomly selected type-2 diabetic patients under regular follow up at the center, and 166 age and sex matched non-diabetic outpatients at the 7th of October teaching hospital. Real-time abdominal ultrasound was performed by two radiologists to examine the abdomen after an overnight fast. Results: About 40% of the diabetic cohort had gall bladder stones as compared to 17.5% of non-diabetic patients. Females were significantly more affected than males. Patients with gall bladder stones were significantly older and had a significantly higher body mass index than those without stones. **Conclusion:** The prevalence of gallstones in Libyan diabetic patients is higher than the rates reported in other parts of the world. Libyan diabetic patients with gallstones tend to be older and more obese than those without gallstones. Duration of diabetes mellitus and type of treatment does not seem to influence the frequency of gall bladder stones among Libyan diabetics.

Key words: *Diabetes, Gallstone, Gallbladder, Obesity, Epidemiology, Libya*

Introduction

Diabetes mellitus (DM) and gall bladder stones (GBS) are both common and costly diseases. In general, GBS are more frequent in females due to hormonal factors. Increasing age, overweight, family history of GBS and type 2 DM are all associated with an increased risk of gallstones [1]. In 1993 Abdulwahab and Karim reported that about 77% of all operations performed at Al-Hawari Teaching Hospital in Benghazi, Libya, were cholecystectomies, with a female to male ratio of 4:1 [2]. In a recent report from Benghazi the prevalence of DM among cholecystectomized patients was 9.9% [3]. Several studies from across the world reported an increased prevalence of GBS in patients with DM [4-8]. How diabetes predisposes to gallstones is not well understood. However, hypertriglyceridemia, autonomic neuropathy (leading to gallbladder hypomotility and biliary stasis) [4] and hyperinsulinemia [1,5] have been suggested as contributing factors to the increased risk of GBS development in diabetics. An Italian study showed that the prevalence of gallstone disease is significantly higher in diabetic patients than in the general population (24.8% vs.13.8%) [6]. Another study from New Zeeland reported a GBS prevalence of 32.7% among diabetic patients as compared to 20.8% in controls [7]. To the best of our knowledge, no data has been reported from Libya on the prevalence of GBS, neither in the general population nor in diabetic patients.

Aims and objectives

The aim of this study was to determine the frequency of GBS among Libyan diabetics in comparison to non diabetic outpatients and to evaluate the possible associated factors in this high risk group.

Patients and methods

A case-control study was performed during 2007. The study involved 161(107 females and 54 males) randomly selected type-2 diabetic patients under regular follow up at Benghazi diabetes and endocrinology center (BDEC). The control group consisted of 166 age and sex matched non diabetic patients (109 females and 57 males) recruited from subjects attending the medical outpatient department of 7th of October teaching hospital for check up.

Patients were interviewed to obtain the following information: age, sex, duration of DM, type of treatment, parity, history of cholecystectomy, history of GBS (patients with previous history of GBS were included), type of GBS (single or multiple), use of oral contraceptives, and history of GBS in first degree relatives. Weight and height were measured and body mass index (BMI) was calculated for each patient. Obesity was defined according to WHO as BMI $\geq$ 30 kg/m². Two radiologists employed real-time ultrasound to examine the abdomen after an overnight fast. Data were analyzed with the Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago, IL). Data were expressed as mean ± standard deviation (SD). Differences between groups were evaluated by using the Chi squared test and independent samples t-test. P-values <0.05 were considered statistically significant.

Results

The mean age of the diabetic cohort was 52.5±11.7 years (50.8±10.3 years for females and 56±13.5 years for males). The mean age of the control group was 49.5±19.9 years (47.7±19 years for females and 52.7±21 years for males).

GBS was observed in 39.75% of the diabetic cohort and in 17.5% of the control (2.27 times higher) (Table 1), the prevalence was significantly higher in female diabetics than in male diabetics (47% vs.26%, p=0.01).

Table 1 Comparison between diabetics and control group

	DM	NO DM	P-value
Number	161	166	
Females	107	109	
Males	54	57	
GBS (%)	39.8%	17.5%	0.000
GBS % in F	46.7%	18.3%	0.000
GBS % in M	25.9%	15.8%	0.18
Mean age (±SD)	52.5±11.7 years	49.5±19.9 years	0.095
Mean age of F (±SD)	50.8±10.3 years	47.7±19 years	0.14
Mean age of M (±SD)	56±13.5 years	52.7±21 years	0.34
Multiple GBS	75% of all GBS	72.4% of all GBS	0.79

Female=F, Male=M, DM= diabetes mellitus, GBS= gallbladder stone, SD= standard deviation

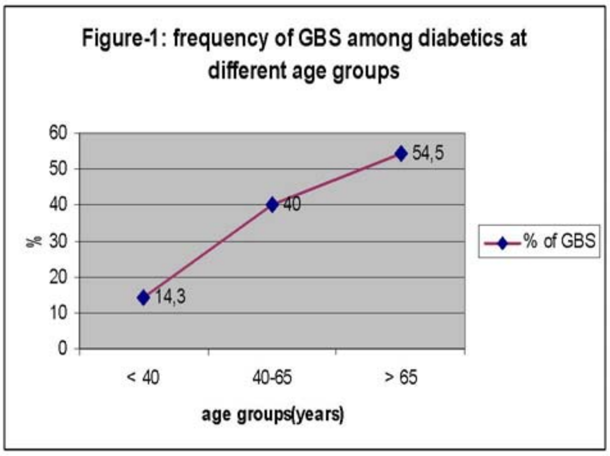
Table 2 Comparison between diabetics with GBS and without GBS

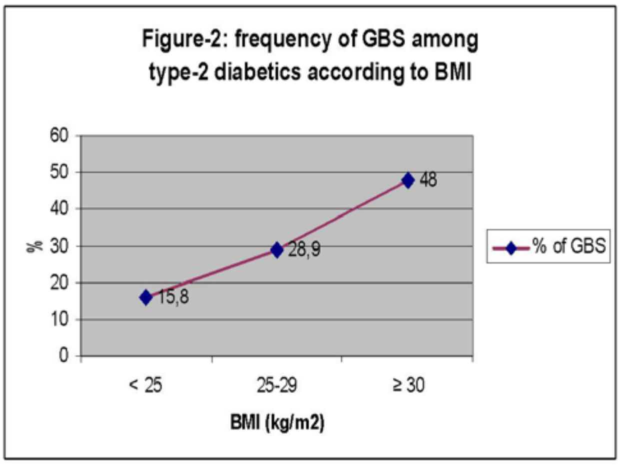
	Diabetics with GBS	Diabetics without GBS	P-value
Females	78%	59%	0.011
Age	55.5± 9.7 years	50.5± 12.5 years	0.007
DM duration(±SD)	12.5±7.7 years	10.6± 6.8years	0.11
Mean Weight(±SD)	84.7±14.9 kg (58-124)	82.2±16.9 kg (51-123)	0.33
Mean BMI (±SD)	34.78±6.29 kg/m²(21.5-55.1)	32.2±7.5 kg/m² (19.1-54)	0.027
OHG	21.9%	21.6%	0.97
INSULIN	21.9%	26.8%	0.47
BOTH	54.6%	46.3%	0.30
F/H	41.2%	27.8%	0.07

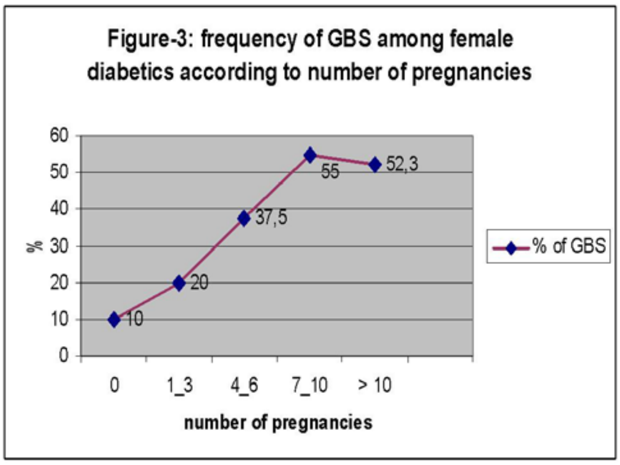
GBS= gallbladder stone, DM=diabetes mellitus, SD= standard deviation, BMI= body mass index, OHG=oral hypoglycemic drugs, F/H= family history

The higher prevalence of GBS among females compared to males was more marked in diabetic patients younger than 50 years (42.5% vs.7.7%, p=0.02) than in those who were 50 years or older (51.8% in females vs. 37.1% in males, p=0.17). In the control group females were also more affected than males (18.3% vs. 15.8%). Diabetic patients with GBS were overall significantly older than those without GBS (mean 55.5 years vs. 50.5 years, p=0.007), (Table 2). Similarly, males with GBS were significantly older than their female counterparts (Table 3). The prevalence of GBS among diabetics progressively increased with age (Figure 1).The age beyond which prevalence of GBS increased significantly was 41 years in females (p=0.01) and 53 years in males (p=0.003).There was no significant difference between diabetic patients with GBS and diabetic patients without GBS regarding duration of DM or type of treatment (oral, insulin or both) (Table 2).

The mean BMI for diabetics with GBS was significantly higher, 34.78+/-6.29, than the mean BMI for diabetics without GBS, 32.2+/-7.5, (p=0.027). Risk of GBS increased significantly when BMI was over 24 kg/m2 (p=0.019) (Figure 2). Moreover, the mean BMI of diabetic females with GBS was significantly higher than the mean BMI of diabetic males with GBS (p<0.001). A family history of GBS was found in 40.6% of patients with GBS and 27.8% of those without, but it was only in females that the difference (48% vs. 24.5%) was significant (p= 0.011). The frequency of GBS progressively increased with number of pregnancies (Figure 3). About 50.5% of multiparus females had GBS as compared to 10% of nulliparus (p= 0.01). Mean parity of females with GBS (10.1+/-3.48; range: 0-17) was significantly higher (p= 0.010) than mean parity of females without GBS (7.7+/-4.7; range: 0-17). About 44% of females with GBS were using oral contraceptives as compared to 42% of females without GBS (p= 0.84, both groups had almost the same mean age, mean duration of DM and mean BMI).







GBS was multiple in 75% of diabetics and 72% of controls, and no significant difference was found between males and females either (p= 0.29). About 73.4% of GBS patients were symptomatic and females were significantly more symptomatic than males (80% vs. 50%, p= 0.025).

Discussion

The prevalence of GBS among Libyan female diabetic patients was significantly higher than in non diabetic female outpatients, but a similar difference was not observed among males. Though no explanation can be offered, it is noteworthy that a similar observation was reported from New Zealand [7]. The rate of GBS in type-2 Libyan diabetics in this study (40%) was higher than that reported from Italy (24.8%) [6] and nearly similar to what was reported from New Zealand (42.1%) in type-2 diabetics [7], even though our patients were younger than the patients in the other two studies (Table 4). This high prevalence rate was maintained even when the sex distribution of the study populations was considered. This might reflect a higher risk of GBS among Libyans in general as a result of other contributing risk factors for GBS, such as genetic predisposition, obesity, multiparity and dietary habits.

Diabetic women were 1.8 times more affected than diabetic men (47% vs. 26%, p=0.01), which agrees with observations of significantly higher prevalence of gallstones among diabetic and non diabetic women compared to men from all over the world [1,2,6,9]. The higher rate in women is probably due to the effects of sex hormones and pregnancy. Estrogen induces an increase in cholesterol secretion while progesterone induces reduction in bile acid secretion [10]. These changes eventually lead to supersaturation of bile with cholesterol, which facilitates gallstone formation. However, the higher prevalence we observed among females became statistically insignificant after the age of 50 when females were only 1.4 times more affected than males (51.8% vs. 37.1%,p-value:0.17) as compared to 5.5 time in patients younger than 50 years old (42.5% vs.7.7%, p=0.02) .

Age also is a well recognized risk factor for the gallstones in both diabetics and non diabetics [1,6,7,8]. The prevalence of GBS in diabetics older than 40 years was about three times higher than that in younger subjects (42% vs. 13%). Generally, patients with GBS were significantly older than those without GBS (55.5 years vs. 50.5 years, p=0.007), and males with GBS were significantly older than females with GBS (62.9 vs. 53.5, p= 0.001). The cutoff age beyond which the GBS became significantly higher was 41 years in females (p= 0.01) and 53 years in males (p=0.003). About three fourths of GBS patients were symptomatic and females were significantly more symptomatic than males (80% vs. 50%); whether females are really more symptomatic or whether they are just more expressive is not clear.

Obesity and overweight are well-known risk factors for the development of gallstones, seemingly due to increased cholesterol synthesis and secretion [1,6,7,8,11]. The risk is particularly high in women [12]. Obesity was more prevalent in GBS diabetics than in non GBS diabetics (77.8% vs. 55.2%). Diabetics with GBS had a significantly higher BMI than those without GBS (34.78 kg/m² vs. 32.2 kg/m², p=0.027). The cutoff BMI associated with significantly increased risk of GBS was 24 kg/m² (p=0.019), which is very near the top of the BMI normal range. Moreover, diabetic women with GBS were significantly more obese than diabetic men with GBS (36.3 kg/m² vs. 29.46 kg/m ², p<0.001).

A family history of GBS has been reported to be an important risk factor for GBS [1,6,7,13]. In our study, a family history of GBS was found in 41.2% of patients with GBS and in 27.8% of those without GBS. The difference bordered on statistical significance (p=0.07). We depended on the patients' recall of family members with GBS, and if instead family members were screened with ultrasound the difference might have been more pronounced. Furthermore, a family history of GBS was significantly more prevalent among female patients with GBS (p=0.011).

Pregnancy is a major risk factor for the development of gallstones [1,7] due to qualitative changes in bile and slowing of gallbladder emptying, which promotes bile stasis. The mean number of pregnancies of diabetic women with GBS was significantly higher than that of diabetic women without GBS (10.1 vs. 7.7, p=0.01). In comparison to nulliparus women, diabetic women who had been pregnant at least once before had a significantly higher prevalence of GBS (10% vs. 50.5%, p=0.01). This higher prevalence can not be attributed to age differences alone, as the mean ages of the two groups were not significantly different (46+/-8.9 vs. 40+/-18.7, p=0.13).

Table 3 Comparison between male and female diabetics with GBS

	All GBS patients	Males with GBS	Females with GBS	P-value
Mean age (±SD)	55.5±9.7 years	62.9± 8.5 years	53.5±9 years	0.001
DM duration (±SD)	12.5±7.7 years	13.7± 7.3 years	12.1± 7.9 years	0.49
Mean weight (±SD)	84.7±14.9 kg	82.5±12.1 kg	85.3±15.6 kg	0.5
Mean BMI (±SD)	34.78±6.29 kg/m²	29.46±4.3 kg/m²	36.3±5.9 kg/m²	<0.001
Symptoms	73.4%	50%	80%	0.025
Multiple GBS	75%	64%	78%	0.29
Family history	40.6%	15.3%	48%	0.03

GBS= gallbladder stone, DM=diabetes mellitus, BMI= body mass index, SD= standard deviation

Oral contraceptive pills (OCP) are also believed to be associated with a slight increase in the risk of gallstone formation. However, in this study OCP did not seem to increase the risk of GBS in diabetic women, as there was no significant difference in the frequency of using OCP between diabetic women with and without GBS (44% vs. 42%, p=0.84), and this is similar to results reported from Italy [6]. It has been shown that the frequency of GBS increased only slightly and transiently after starting oral contraceptives, and then the effect disappeared after 10 years [14]. Another study stated that the use OCP only marginally affects the incidence of GBS if at all [15]. On the other hand, the risk of GBS is highest when the estrogen dose is >50 μg [16], while the commonly used OCP in Libya over the past 10 years contain only 35 μg of estrogen, which might not be high enough to induce formation of a lithogenic bile.

Table 4 comparison between GBS frequency among type-2 diabetics in Libya, Italy and New Zealand

	Libya	**Italy** [6]	**New Zealand** [7]
Number of patients	161	1337	309
Mean age	52.5±11.7 years	NR	57.9 years
Mean age for females	50.8±10.3 years	65±11 years	NR
Mean age for males	56±13.5 years	63± 11 years	NR
GBS in all	39.8%	25%	42.1%
GBS in Females	46.7%	29%	48.6%
GBS in Males	25.9%	22%	33.3%

GBS= gallbladder stone, NR= not reported

Although the duration of DM in GBS patients (12.5+/-7.7 years) was slightly longer than the duration in diabetics without GBS (10.6+/-6.8 years), this did not appear to affect the frequency of GBS, as the difference was not statistically significant. The type of treatment does not seem to influence the frequency of GBS as there was no significant difference between GBS and non GBS diabetics regarding the type of treatment (oral, insulin or both).

Multiple GBS were detected in 75% of the cases, and there was no significant difference between diabetics and non diabetics or males and females regarding multiplicity of stones.

Conclusions

Libyan diabetic patients had a significantly higher prevalence of GBS than non diabetics (~2.3 times). Female diabetic patients were significantly more affected than males and the prevalence significantly increased with age particularly in males. Older age (>41 years in females and >53 years in males), high BMI (>24 kg/m²), female gender, and parity were the most significant risk factors for GBS in Libyan diabetic patients. By contrast, duration of DM, the type of hypoglycemic agent, and the use of OCP did not seem to influence the frequency of GBS among type 2 diabetics. Multiple GBS were the most common kind of GBS in diabetics, and the frequency of multiple and single GBS was similar among diabetics and non diabetics.

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