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ORIGINAL ARTICLE

Prevalence of gallbladder disease in Type 2 DM and prediabetes in Mogadishu Somalia: A single center experience.

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ABSTRACT… Objective: To assess the clinical and ultrasonographic findings of gallbladder disease in diabetic, prediabetic, and non-diabetic patients. **Study Design:** Retrospective Cross-Sectional Study. **Setting:** Mogadishu Somali Turkey Training and Research Hospital, Mogadishu Somalia. **Period:** January 2017 and June 2019. **Material & Methods:** T2DM, prediabetes, demographic data, and gall bladder findings. **Results:** The study included 1,020 patients, 65.6% of whom were female, with a mean age of 50.51 ± 17.98. In our study, in which the number of non-diabetic people was 425 (41.7%), the rate of T2DM was found to be 36.3%, and the rate of prediabetic patients was found to be 22.1%. The frequency of T2DM (41%) and prediabetes (23.9%) was found to be higher in men with GBD than in women (33.8% and 21.1% in women, respectively). Increased gallbladder wall thickness frequency was also found to be more common in the T2DM and prediabetic groups than in the non-DM group ($p<0.001$). **Conclusions:** Patients with GBD have a significantly increased T2DM frequency (one in 3 patients) and prediabetes (one in five patients). More than half of patients have 2 or more gallstones, and a third have bile sludge. Impaired glucose tolerance is considered to be a major factor in the development of GBD in Somali patients.

Key words: Africa, Cholelithiasis, Diabetes Mellitus, Gallstones, GBD, Impaired Glucose Tolerance, Somalia.

INTRODUCTION

Gallbladder disease (GBD) is a worldwide problem that necessitates surgery and drives up healthcare costs. GBD affects 10-20% of adult global population, increasing morbidity, mortality, and socioeconomic costs.[1-3] However, its prevalence varies greatly between different populations.

Besides from gallstone recurrence, significant complications such cholecystitis, cholangitis, and pancreatitis affect patients' health and quality of life after cholecystectomy.[4] While obesity[1,2,4] type 2 diabetes (T2DM)[5] and smoking are prominent risk factors for gallstones; alcohol[4,6] and coffee consumption[4,7] have been noted as protective factors in traditional observational studies. Gallstones are the main risk factor for gallbladder cancer (GBC)[8,9] and are present in approximately 90% of cases in high-risk areas for cancer development.[10] However, only a minority of people with gallstones develop GBC. The recommended treatment for symptomatic gallstones is cholecystectomy (i.e., surgical removal of the gallbladder); however, not all cases of gallstones cause symptoms and cholecystectomy can lead to medical complications and side effects such as increased risk of biliary tract injury or other digestive diseases in the long term.[11,12]

A history of DM[13] is a strong risk factor for GBD, which is also an important risk factor for pancreatitis.[14] Cholelithiasis may progress more quickly in diabetic patients due to chronic and severe gallbladder infections. The prevalence of GBD reported worldwide in patients diagnosed with T2DM is approximately 36.2%.

The epidemiology and characteristics of GBD differ between different races. For example, GBD

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is more prevalent in Hispanic and Native American populations than in Central Asian and African ones.[15] In many African countries, an increase in the frequency of cholelithiasis has been observed due to rapid urbanization and the adoption of a western-style diet.[16]

This study aims to compare diabetic, prediabetic, and non-diabetic patients diagnosed with GBD at the Mogadishu Somali Turkey Training and Research Hospital, Mogadishu Somalia.

MATERIAL & METHODS

Our study was retrospective cross-sectional. Between January 2017 and June 2019, our study included patients who attended outpatient care at the Mogadishu Somali Turkey Training and Research Hospital, Mogadishu Somalia. Age >18 and no known liver disease were inclusion criteria. The study excluded patients with incomplete clinical histories, urgent surgical indications, and inadequate US imaging reports. The study started after the Ethics Committee approved it (Decision dated 28.05.2019, MSTH/ 1335).

The patient symptoms consisted of post-prandial abdominal pain, dyspepsia, nausea-vomiting, and patients referred to the radiology clinic with an abdominal US indication for control purposes. General clinical history, physical examination, T2DM blood tests, fasting lipid profile and abdominal US results were obtained retrospectively from the electronic patient registry system of the hospital. T2DM and pre-diabetes diagnosis, glycemic findings, and targets for lipids were evaluated according to the criteria set by the American Diabetes Association (ADA).[17]

The Mindray Digital Ultrasound Imaging System (Model DC 8®; Shenzhen Mindray Biomed Electronics, Shenzhen, China) was used for all examinations. To reduce gastric and intestinal gas and stretch the gallbladder, patients fast overnight. The stomach and duodenum were checked for food particles and fluid to ensure the patient was fasting overnight. GB measurements (mm) were taken with the probe placed in the longitudinal and horizontal planes in the right hypochondrial and midclavicular line. Length (L) and gallbladder wall thickness (GBWT) were taken in the longitudinal plane with breathing stopped. Width (W) and height (H) were taken in the horizontal plane after the probe was rotated 90° from the longitudinal view to obtain a maximum transverse view. Gallbladder volume (GBV) (cm3) was calculated using the prolate ellipsoid formula ($L \times H \times W \times 0.523$), which is the simplest and most widely accepted method for clinical practice recommended by Dodds et al.[18]

Since there are no reference values for Somali residents for increased gallbladder size, it was estimated using the study conducted by Oluseyi et al. in Nigeria in 2016.[19] An increase in gallbladder wall thickness of 3 mm was considered a pathological increase.[20] Evaluations regarding gallstones and sludge were recorded for all patients.[21] Our study's gallbladder USG measurements were all conducted by experienced radiologist who had no knowledge of the study.

Statistical Methods

SPSS 27.0 and Modeler 18.0 (IBM Corporation, Armonk, New York, United States) programs were used in the analysis of variables. The conformity of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test, while the variance homogeneity was evaluated with the Levene test. In comparing more than two groups with each other according to quantitative data, the Kruskal-Wallis H Test was used with Monte Carlo simulation technique results, and Dunn's Test was used for post hoc analysis. In the comparison of categorical variables with each other, the Pearson Chi-Square and Fisher-Freeman-Halton tests were tested with the Monte Carlo Simulation technique and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. Logistic Regression, Support Vector Machine, Random Forest, K-nearest Neighbor Algorithm, Simple (Native) Bayes Classification and Neural Network (Multilayer Perceptron-Radial Basis) were used to find and predict the variable with the highest significance of the groups. The results of Neural Network (Multilayer Perceptron) analysis, which is the most successful model among these methods,

were used. The Gradient descent optimization algorithm, hyperbolic tangent as hidden layer activation function, hyperbolic tangent function, exponential output layer activation function, and hyperbolic tangent softmax function were used. The Mini-batch method was used for traning data selection, of which 70% was the Traning set and 30% the Testing set. Quantitative variables were expressed as mean (standard deviation) and Median (Percentile 25 / Percentile 75) in the tables, while categorical variables were shown as n (%). Variables were examined at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

RESULTS

A total of 1,020 patients, 65.6% of whom were women, with a mean age of 50.51 ± 17.98 years were included in the study (Table-I). In our study, in which the number of non-diabetic people was 425 (41.7%), the rate of T2DM was found to be 36.3%, and the rate of prediabetic patients was found to be 22.1%. Although the frequency of T2DM was 36.3%, the rate of prediabetic patients with insulin resistance was 22.1%. The frequency of T2DM (41%) and prediabetes (23.9%) was higher in men with GBD than in women (33.8% and 21.1% in women, respectively). While the appearance of millimetric gallstones was detected in 233 (29.9%) of the patients, gall sludge was observed in 354 (34.7%) of them. Increased gall bladder size was found in 201 (19.7%) of the patients and increases in wall thickness in 268 (26.3%) (Table-I).

Single gallstones were detected in 235 (30.3%) patients, while more than 2 stones were found in 509 (65.6%) patients. In 917 (89.9%) patients, bile ducts were found to be normal or could not be visualized by US (Table-I). The prevalence of prediabetes (62.7%) and T2DM (61.1%) in women was lower than that in the non-diabetic group (71.1%) ($p = 0.009$ and $p = 0.043$, respectively). In males, pre-DM (37.3%) and T2DM (38.9%) frequencies were found to higher compared to those in the non-diabetic group (28.9%) ($p = 0.009$ and $p = 0.043$, respectively) (Table-II).

T2DM, prediabetic and non-diabetic age distributions were different from each other. T2DM patients were significantly older than the other groups, while the youngest group consisted of non-diabetic individuals ($p<0.001$) (Table-II).

HDL-C and TG levels of T2DM patients were similar to those in other groups, while Total-C and LDL-C levels were significantly higher than those in non-diabetes and prediabetes groups. Gall bladder size of T2DM patients and prediabetic patients was greater than that of non-diabetic patients. The incidence of single stones in the non-diabetic group was higher than in pre-diabetic patients, but it was lower than in T2DM patients (Table-II).

Increased biliary tract width was most frequently detected in the T2DM group, but with a similar frequency to that in the prediabetes group. The frequency of gallbladder sludge was similar among the groups. Increased gallbladder wall thickness frequency was also found to be more common in T2DM and prediabetic groups than in the non-DM group ($p<0.001$) (Table-II).

In our study, in the Neural Network (Multilayer Perceptron) analysis used to predict T2DM, prediabetes or non-DM groups, one of the significant variables in Table-I; independent variables such as age, LDL-C, Total-C, stone size, gallbladder size, number of stones, gender, and gallbladder wall thickness were included in the model.

According to this model, traning set success rates were found to be 79.2%, the correct prediction rate for non-DM positivity was found to be 68.4% for the T2DM group, and 17.4% for the prediabetes group, respectively. The overall accuracy rate of the model was found to be 61.7%. The success rates for the test set were found to be 77.2%, 58.5%, and 4%, respectively. For this model, the significance rates of variables were determined to be 100%, age, 89.5% LDL-C and 77.6% Total-C, respectively (Table-III).

DİSCUSSİON

This study's aim was to evaluate T2DM and prediabetes prevalence and discuss GBD findings. In this study, we found that T2DM and prediabetic disease is common in patients diagnosed with GBD.

	N (%)					
Groups						
Non-Diabetic	425 (41.7%)					
T2DM	370 (36.3%)					
Pre-Diabetic	225 (22.1%)					
Gender						
Female	669 (65.6%)					
Male	351 (34.4%)					
Gallbladder Size						
Normal	819 (80.3%)					
Increased	201 (19.7%)					
Stone Size						
Milimetric	233 (29.9%)					
3-10 mm	113 (14.5%)					
10-20 mm	278 (35.7%)					
20-50 mm	140 (18.0%)					
>50 mm	14 (1.8%)					
Stone Count						
Single	235 (30.3%)					
2	32 (4.1%)					
>2	509 (65.6%)					
Gallbladder Sludge						
Yok	666 (65.3%)					
Var	354 (34.7%)					
Bile Duct						
Normal or not visualized	917 (89.9%)					
Dilated	103 (10.1%)					
Gallbladder wall thickness						
Normal	752 (73.7%)					
Increased (≥5 mm)	268 (26.3%)					
	Mean (SD.)	**Min.**	**Q1**	**Q2**	**Q3**	**Max.**
Age	50.51 (17.98)	18.0	36.0	49.0	65.0	98.0
Glucose	130.67 (63.25)	70.0	95.0	108.0	141.0	568.0
HbA1c	6.46 (1.86)	4.3	5.2	5.7	7.1	18.0
TG	146.90 (87.57)	43.0	87.0	119.0	178.0	936.0
HDL-C	51.16 (14.77)	25.0	40.0	49.0	60.0	119.0
Total-C	197.91 (41.80)	96.0	166.0	201.0	221.0	467.0
LDL-C	117.60 (35.61)	38.0	91.0	117.0	137.0	373.0

SD: Standard Deviation, Q1: Percentile 25, Q2: Percentile 50 (median), Q3: Percentile 75

Table-I. Demographic, biochemical and ultrasonographic findings of the patients.

	Non-Diabetic (I)	T2DM (II)	Pre-Diabetic (III)	P-Value	Pairwise Comparisons		
	(n=425)	(n=370)	(n=225)		I-II	I-III	II-III
	n (%)	n (%)	n (%)				
Gender				0.008 c			
Female	302 (71.1)	226 (61.1) (33.8% in male)	141 (62.7) (21.1% in female)		0.009	0.043	ns.
Male	123 (28.9)	144 (38.9) (41% in male)	84 (37.3) (23.9% in male)		0.009	0.043	ns.
	Median (Q1 / Q3)	Median (Q1 / Q3)	Median (Q1 / Q3)				
Age	42 (31 / 52)	61 (49 / 72)	46 (35 / 60)	<0.001 k	<0.001	0.004	<0.001
Glucose	93 (88 / 97)	156.5 (137 / 207)	111 (106 / 117)	<0.001 k	<0.001	<0.001	<0.001
HbA1c	5.2 (5 / 5.3)	7.6 (7 / 9.5)	5.8 (5.6 / 6)	<0.001 k	<0.001	<0.001	<0.001
TG	114 (81 / 178)	125 (92 / 182)	123 (88 / 171)	0.616 k	ns.	ns.	ns.
HDL-C	49 (40 / 68)	49 (41 / 58)	49 (41 / 58)	0.832 k	ns.	ns.	ns.
Total-C	201 (163 / 215)	207 (178 / 233)	185 (159 / 224)	<0.001 k	<0.001	0.999	<0.001
LDL-C	117 (88 / 129)	130 (101 / 151)	108 (84 / 141)	<0.001 k	<0.001	0.859	<0.001
	n (%)	n (%)	n (%)				
Gallbladder Size				<0.001 c			
Normal	397 (93.4)	242 (65.4)	180 (80.0)		<0.001	<0.001	<0.001
Increased	28 (6.6)	128 (34.6)	45 (20.0)		<0.001	<0.001	<0.001
Stone Size				<0.001 ff			
Milimetric	86 (28.0)	101 (33.7)	46 (26.9)		ns.	ns.	ns.
3-10 mm	65 (21.2)	29 (9.7)	19 (11.1)		<0.001	0.008	ns.
10-20 mm	96 (31.3)	101 (33.7)	81 (47.4)		ns.	0.001	0.005
20-50 mm	53 (17.3)	63 (21.0)	24 (14.0)		ns.	ns.	ns.
>50 mm	7 (2.3)	6 (2.0)	1 (0.6)		ns.	ns.	ns.
Stone Count				0.001 c			
Single	94 (30.8)	105 (35.0)	36 (21.1)		ns.	0.033	0.004
2	16 (5.2)	14 (4.7)	2 (1.2)		ns.	ns.	ns.
>2	195 (63.9)	181 (60.3)	133 (77.8)		ns.	0.003	<0.001
Gallbladder Sludge				0.366 c			
Yok	271 (63.8)	252 (68.1)	143 (63.6)		ns.	ns.	ns.
Var	154 (36.2)	118 (31.9)	82 (36.4)		ns.	ns.	ns.
Bile Duct				<0.001 c			
Normal	403 (94.8)	315 (85.1)	199 (88.4)		<0.001	0.005	ns.
Dilated	22 (5.2)	55 (14.9)	26 (11.6)		<0.001	0.005	ns.
Gallbladder wall thickness				<0.001 c			
Normal	355 (83.5)	235 (63.5)	162 (72.0)		<0.001	0.001	0.033
Increased (≥5 mm)	70 (16.5)	135 (36.5)	63 (28.0)		<0.001	0.001	0.033

[c] Pearson Chi-Square Test (Monte Carlo); Post Hoc Test: Benjamini-Hochberg correction, [ff] Fisher-Freeman-Halton Exact Test (Monte Carlo); Post Hoc Test: Benjamini-Hochberg correction, [k] Kruskal-Wallis H Test (Monte Carlo), Post Hoc Test : Dunn's Test, Q1: Percentile 25, Q3: Percentile 75

Table-II. Characteristics of diabetic, prediabetic and non-diabetic groups.

Variable Importance		Sample (Holdout)	Predicted			
Independent Variable	Normalized Importance		non-DM	DM	Pre-Diabetic	Percent Correct
		Training (%70)				
Age	100%	non-DM	179	37	10	79.2%
LDL-C	89.5%	DM	58	141	7	68.4%
Total-C	77.6%	Pre-Diabetic	58	42	21	17.4%
Stone Size	40.6%	Overall Percent	53.3%	39.8%	6.9%	61.7%
Gallbladder Size	37.8%	Testing (%30)				
Stone Count	32.3%	non-DM	61	15	3	77.2%
Bile Duct Size	18.3%	DM	35	55	4	58.5%
Gender	10.9%	Pre-Diabetic	24	24	2	4.0%
Wall Thickness	7.5%	Overall Percent	53.8%	42.2%	4.0%	52.9%
Neural Network (Multilayer Perceptron), Hidden Layer Activation function: Hyperbolic Tangent- Output Layer Activation function: Hyperbolic Tangent, Dependent Variable: Groups						

Table-III. Artificial neural network analysis used to predict patient groups.

In our study, the frequency of T2DM was found to be 36.3%, and the rate of pre-diabetic patients with insulin resistance was found to be 22.1%. The frequency of T2DM (41%) and prediabetes (23.9%) was higher in men with GBD disease than in women (33.8% and 21.1% in women, respectively).

The epidemiology and characteristics of GBD differ between races. For example, the prevalence of GBD is higher in Hispanic and indigenous populations in America, and lower in Central Asian and African populations.[15] Previous studies have suggested an increase in the frequency of GBD and cholecystectomy associated with urbanization and the adoption of western lifestyle habits. The rapid urbanization and adoption of a western-style diet have increased the frequency of cholelithiasis in many African countries.[16] Over the years, there seems to have been a remarkable rate of increase in T2DM and correspondingly a significant increase in the frequency of GBD in Somalia.

45 million adults (20-79) in the African Region have Impaired Glucose Tolerance (IGT) that increases the risk of developing T2DM. It is estimated that this figure will reach 110 million by 2045. The International Diabetes Federation (IDF) African Region has the highest percentage of undiagnosed people in all IDF regions, and 60% of adults living with diabetes do not know that they have it. Considering that we found the frequency of T2DM to be 36.3% and pre-diabetes prevalence to be 22.1% in patients with GBD in our study, overt or impaired glucose tolerance is an important finding in one of every two patients with GBD.

Current evidence supports pathophysiological models in which GBD and IR mutually reinforce one other, potentially promoting excessive weight gain in people who are predisposed to obesity. Bile acids, enterohormones, hepatokines, and adipokines, according to this new paradigm, mediate a varied communication between different tissues to coordinate glucose, lipid, and energy homeostasis in order to maintain appropriate body composition and insulin sensitivity. In addition to its traditional functions in fatty food digestion and absorption, increasing evidence suggests that the gallbladder plays a physiological role in glucose, lipid, and energy homeostasis, and that both GBD and cholecystectomy reduce insulin sensitivity.[22]

GBD, obesity, and insulin resistance (IR) have traditionally been considered to have largely unidirectional pathophysiological relationships. Obesity is a risk factor for both GBD and IR, and the two complications have a fairly independent relationship. However, current knowledge

describes a more complex situation in which obesity promotes both GBD and IR, but at the same time GBD increases IR, and both conditions act as a cause of GBD.[2,23] The frequency of IR increases with age and this situation increases the frequency of T2DM development due to decreased endocrine pancreatic functions, especially in people over 50 years old. Diabetes prevalence also increases with age. However, most people living with diabetes in Sub-Saharan Africa (SSA) countries are in the 45-64 age group, unlike developed countries where the highest diabetes prevalence is 65 years and over.[24] According to the data of the IDF group, it is estimated that 19 million adults (20-79) in the African Region lived with diabetes in 2019, and this number will increase to 47 million by 2045.

In a recent study, Khan et al. evaluated the T2DM epidemiology for the continents of Asia, Europe, America and Africa as opposed to economic classification. In this study, the prevalence of T2DM was determined to be 7,360/100,000 people in South Africa and it was noteworthy that this rate was similar to that globally. It has been observed that the age of onset of a new diagnosis is also a little earlier among males and its frequency tends to increase with increasing age, with the incidence peaking at the age of 55-59.[25] In the same study, it was emphasized that men showed a slightly higher prevalence than women, but this difference was not significant enough. In our study, in line with this information, the prevalence of T2DM (41%) and prediabetes (23.9%) was found to be higher in men with GBD than in women.

Epidemiological studies have been used to determine the prevalence and relationship between diabetes mellitus (NIDDM) and GBD. GBD has been found to be more frequent in diabetics.[26,27] Several studies that examined at the outcomes of cholecystectomy in relation to hospital volume and found that high-volume facilities have lower morbidity and costs.[28,29] The South African health system is dealing with four epidemics at the same time: communicable diseases, especially HIV, maternal mortality, malnutrition, and the rising burden of noncommunicable diseases.[30] Over the years, uncontrolled HbA1c levels have been shown to be best controlled with intensive insulin treatment. This treatment method not only decreases patient quality of life but also burdens the country's economy. The exponential rise in cholecystectomies over the last decade has put a strain on an already overburdened system. These data necessitate consensus on GBD risk reduction strategies, including community education and weight-loss programs.

In a study by Méndez-Sánchez et al., the frequency of T2DM was found to be 14.3%.[31] In a similar Swedish study, the prevalence was found to be 15%.[32] In this study, it was found that the frequency of T2DM was 36.3% in patients with GBD and 22.1% were diagnosed with pre-diabetes. However, it is difficult to interpret these rates with the results found in patients with GBD.

Ultrasonography (USG) plays an important role in the GBD diagnosis protocol. It is a low-risk and low-cost diagnostic approach that allows widespread screening. USG is a sustainable method in low-resource countries, and it can improve patient care and diagnostic capabilities in remote areas.[33] A precise point-of-care diagnosis using US has been found to assist in rapid diagnosis and treatment in rural international settings.

Our study's limitations come from its retrospective cross-sectional design. Diabetes prevalence and gall bladder characteristics were evaluated in patients with only a GBD diagnosis. Since the general prevalence of T2DM and IGT in Mogadishu, which still does not have a detailed screening program, was not known, it was not possible to evaluate the effect of diabetes on the development of GBD. However, the fact that GBD patients had a much higher prevalence of DM than expected is considered significant.

Since we could not evaluate the results of cholecystectomy and the follow-up of patients with GBD in our study, it was not possible to interpret the frequency of GBC, polyps, morbidity and mortality, and gallstone characteristics. The patients' region may also cause confusion in the normal population registration and identity

information. This is important since the same patient can be evaluated under different names, thus leading to double counting. Currently, we think this is the largest study in Mogadishu evaluating the relationship between GBD and DM. A larger screening program for GBD, which is a major cause of morbidity and mortality in the region, would help interpreting our findings.

CONCLUSION

In conclusion, there is a significantly increased T2DM frequency in patients with GBD (one in 3 patients) and prediabetes (one in five patients). More than half of the patients have more than 2 gallstones and one third of them have the appearance of bile sludge. Healthy nutrition and exercise should be among the main preventive measures advised for the development of a healthy society in Somalia to prevent impaired glucose tolerance, which is thought to be a significant factor leading to the development of GBD.

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