UTRASONOGRAPHIC EVALUATION OF GALLBLADDER DISEASES IN PATIENTS WITH DIABETES MELLITUS TYPE TWO ATTENDING AL-NASRIA DIABETIC CENTER

Dr. Haider Mohammed AL-yasiri*, M.B.Ch.B. ,D.M., F.I.C.M.S*
Dr.Kadhim mohan manhil Al-majedy, M.B.Ch.B. ,D.M., F.I.C.M.S*
Dr. Majeed mohan Al-hammamy, M.B.Ch.B. ,D.M., F.I.C.M.S*

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ABSTRACT

Background

little is known about the association of gallbladder disease and diabetes in Iraq. the aims of this study are study the prevalence of GBD in patients with type two diabetes mellitus attending Al-nasria diabetic center.

Patients and methods

Two hundred patients with type two diabetes mellitus were the test group consist of 116 female and 84 male with 57±22 years old in average and two hundred non-diabetic persons as a control group consist of 120 female and 80 male with 52±32 years old in average. Both case and control were examined by ultrasonograghic study to find the GBD.

Results

The frequency of GBD was 35% in patients with type two DM and 15% in non- diabetic subjects. The frequency of GBD in diabetic patients whose BMI was more than 25 kg/m^2 was significant increased. There is a significant increase in GBD with increase of duration of diabetes and increased level of Hb A1c. There was no significant difference in effect of age , parity , family history of GBD between diabetes and non-diabetic subjects.

Conclusion

The prevalence of GBD increase with type two diabetes by two fold in comparison to that of non-diabetic subjects. The risk of GBD increase with increased duration of diabetes mellitus and HbA 1c level.

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* Department of Internal Medicine - College of Medicine - Thi Qar University

INTRODUCTION

Gallstone disease (cholelithiasis) has been identified as one of the diseases of civilization and modern affluent lifestyles of the developed nations Although a number epidemiological studies have shown that the prevalence of gallstones is higher in affluent societies than in developing countries where the population still consumes a traditional diet (Brett and Barker, 1976 Burkitt and Tunstall, 1975; Heaton, 1979), and other research has been shown that gallbladder disease) GBD) prevalence can differ substantially between communities that differ in culture and in diet.

The risk factors of GBD

The risk factors for the development of cholelithiasis include irreversible factors-female sex and advancing age, and reversible factors-obesity, repeated pregnancy, use of contraceptive pills, a family history of gallstones, smoking, diabetes mellitus, plasma lipids and dietary factors, chronic liver disease and possibly major abdominal surgery Further from literature it is clear that several factors, such as supersaturation of bile cholesterol, nucleation and growth of cholesterol crystals, gallbladder mucin, and altered gallbladder motility have been studied extensively.

Diabetes mellitus as a risk factor

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Asymptomatic period of hyperglycemia, being on an average of 5 to 7 years, many individuals tend to have complications at the time of diagnosis, which are macrovascular. Amongst various types of neuropathy, autonomic neuropathy, although a well recognized complication, has been given less attention. In addition to manifestations in many other systems, autonomic neuropathy gives rise to varied manifestations in the gastrointestinal tract i.e. gastropathies, nocturnal diarrhoea, oesophageal dysmotility, constipation and gallbladder dysfunction, being consequence of vagal neuropathy leading to reduced G.I. motility. Duration of diabetes mellitus is positively related to prevalence of gallbladder disease, the type of therapy has no association and the fasting plasma glucose concentration is inversely associated with gall bladder disease. Gallbladder involvement in diabetic autonomic neuropathy is in the form of high incidence of gall stones and a significant increase in gall bladder volume[with poor concentration and poor visualization, with lack of symptoms of gallbladder diseaseThe present study aims to find out the prevalence of gallbladder disease in type 2 diabetes, correlation of gallbladder disease with duration of diabetes and comparison of gallbladder dysfunction in patients with and without autonomic neuropathy as well as normal individuals. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially the eyes kidneys, nerves, heart, gallbladder and blood vessels. Digestive system dysfunction is also an important contributor to morbidity of this disease. Diabetic subjects are reported to have a two to three fold increase in the prevalence of cholesterol gallstone. Inadequate emptying of gallbladder and increased fasting gallbladder volume has been reported in various studies . other several studies examined the relation between DM and GBD. 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.

The role of ultrasound imaging in our study

US remains the method of choice for detection of gallstones, offering several advantages: high sensitivity and accuracy (> 95%) noninvasiveness, the option of performing a bedside examination, lack of ionizing radiation, relatively low cost, and the ability to evaluate adjacent organs. The characteristic findings of gallstones at US are a highly reflective echo from the anterior surface of the gallstone, mobility of the gallstone on repositioning the patient (typically in a decubitus position) In the present study an effort is made to determine prevalence of gallbladder disorder like gallstones, cholecystitis in type2 diabetic patients with the help of ultrasonography included all type two diabetic patients that attended Al-nasria diabetic center. It was correlated with age, sex, weight and duration of diabetes and to compare the gallbladder disease in diabetics with age, sex matched with healthy persons (control group) .

AIM OF THE STUDY

1. We designed a case control study to determine the prevalence of gallbladder disease in a group of subjects with type two DM and in a control group without diabetes mellitus . Both groups were comparable for sex , age , and body mass index .
2. To examine the relationship between the prevalence of gallbladder disease and the severity of glycemia among diabetic individuals and duration of diabetes mellitus .

PATIENTS AND METHOD

This study performed in the Al-Nasria diabetic center from April 2010 –October 2011. We include all patients with type two DM attending the diabetic center. Two hundred patients with type two diabetes mellitus were the test group consist of 58 females and 42 males and was 57 $\pm$ 22 year old in average and Two hundred non-diabetic persons as a control group consists of 60 females and 40 males with 52 $\pm$ 35 year old in average . The age in both groups was range from 30 – 90 years . All subjects in test group were fulfilled the WHO criteria of diabetes mellitus .

The WHO criteria for diagnosis of diabetes mellitus :

1. Symptoms of diabetes plus random blood glucose concentration $\geq$ 200 mg/dl.
2. Fasting plasma glucose > 126 mg/dl .
3. Two-hour plasma glucose $\geq$ 200 mg/dl during the oral glucose tolerance test .

In addition the subjects did not meet these criteria but who were being treated with either oral hypoglycemic drugs or insulin were considered to have some form of diabetes . Subjects were considered to have type two diabetes mellitus who had the followings :

1. Developed diabetes after the age of 30 years .
2. Individual was not treated by insulin therapy initially .
3. There was no history of diabetic ketoacidosis documented by previous investigations .

The subjects with onset of diabetes prior to the age of 30 or treated initially by insulin

or with history of diabetic ketoacidosis were considered as insulin dependant diabetes mellitus and excluded from the study . Individuals who had been diagnosed as having diabetes were asked about the date of their diagnosis and duration of disease and were calculated as current age minus self reported age at diagnosis . Blood samples were drained for determination of hemoglobin HbA_{1C} level and any patient with heamoglobinopathy by history or available blood picture excluded from the study . The control group included individual who did not have history of diabetes mellitus and any symptom or sign of diabetes mellitus and blood samples were taken for measurement of fasting blood sugar and any persons with FBS >126 mg/dl was excluded from the study . Individuals in both case and control groups were asked about family history of GBD or previous cholecysectomy and in females about the number of pregnancies . The body mass index "BMI" was calculated by dividing weight in "kilograms" by height "meters" square. Blood samples were taken in morning following at least a 12 hour fast . Gallbladder ultrasonography was performed by trained operator unaware of the subject history . Gallstones were defined as mobile echoes in gallbladder lumen and cases of cholecystectomy as individuals without a gallbladder at ultrasound and with an abdominal scar .

The final gallbladder status was recorded as follows :

1. Normal at ultrasonography .
2. presence of gallstones at ultrasonography .
3. presence of biliary sludge at ulttrasonography .
4. previous cholecystectomy .

Gallbladder disease was defined as condition 2 or 4 .

This study was conducted in 2 phases :

- In the first phase we compared between case and control group to determine the prevalence of gallbladder disease in patients with type two diabetes mellitus (case) in comparison with individuals without diabetes (control) both groups were comparable for sex , age , and BMI .
- The second phase was a comparison study within diabetic subjects to determine the effect of duration of NIDDM and fasting glycemia , type of therapy and level of hemoglobin A_{1C} on prevalence of gallbladder diseases .

Statistical Analysis

The statical significance of an association between two variables was assessed by Chi-square (X^2) test of independence . An estimate was statistically significant if its calculated value was less than $P < 0.05$ level of significance with 95% confidence .

RESULTS

Figure 1 : Shows the prevalence of gallbladder disease in subjects with type two diabetes mellitus is more frequent than in non-diabetic persons . It is 32% in the diabetic subjects compared to only 15% in non-diabetic subjects (P-value < 0.05) (table 1) .

Figure2 : Shows the prevalence of gallbladder disease was significantly associated with age. It shows that the prevalence statistically increased with increasing age in both diabetic and non-diabetic subjects . There is a mild difference between the two groups but it is not statistically significant (P value > 0.05) (table 2) .

Figure3 : Shows the prevalence increased with increasing BMI in both diabetic and non-diabetic subjects. There is no significant difference in prevalence of

GBD when BMI less than 24kg/m^2 (15.4% Vs. 11.1% P value > 0.05) . But the prevalence increased in diabetic subjects when BMI is more than 25kg/m^2 as compared to that of non-diabetic subjects (32.6%) Vs. 11.4% , P value < 0.02) (table 3) .

Figure 4 : Shows the frequency of GBD in both diabetic and non-diabetic subjects was increased in subject with positive family history of GBD (57.9% , 38.5% respectively) as compared to that of subjects without family history of GBD (25.9% , 11.5% respectively) but there was no statistical significant difference between diabetic and non-diabetic subjects (P value > o.05) (table 4) .

Figure 5 : Shows that the GBD prevalence in diabetic patients was significantly associated with females sex (36.2% in diabetic Vs. 13.3% in non-diabetic subjects , P value < 0.04) in comparison to that of males (26.2% in diabetic Vs . 17.5% in non-diabetic subjects , P value > 0.05) (table 5) .

Figure6 : Shows the prevalence of the GBD increased with increasing parity of women in both diabetic and non-diabetic subjects from (23.7% and 12.5% respectively in women with parity $\leq$ 3 to 28.7% and 14.6% respectively in women with parity > 3) . There is a mild difference between the two groups but statistically not significant , (P value > 0.05) (table 6) .

Figure 7 : Shows the prevalence of GBD by duration of diabetes in years . The prevalence of GBD increased from (30% to 55% and 60% when duration of diabetes increased from less than 5 years to 5 – 10 years and more than 10 years respectively , P value < 0.04) (table 7) .

Figure8 : Shows a mild difference in the prevalence of GBD between diabetic patients treated with insulin to that patients on OHD (23.7% Vs . 37.1% respectively) but this difference was not statistically significant (P value > 0.05) (table 8) .

Figure 10 : Shows the prevalence of GBD was increased from 3.1% in diabetic patients with Hb_{A1C} level < 6% to 6.3% Hb_{A1C} level 7-8% and to 28.1% at Hb_{A1C} level > 10% . The Hb_{A1C} level is strongly associated with increased risk of GBD in diabetic subjects (P value < 0.03) (table 10) .

DISCUSSION

The idea behind this study is to find the frequency of GBD in type two diabetes mellitus in comparison to that of control group and to examine the effect diabetic subgroup . Our study shows that the frequency of GBD in diabetic patients was (32%) in comparison to control (non-diabetic subjects) (15%) . The pathophysiological basis of increased prevalence of GBD in diabetes mellitus is uncertain. Factors were suggested to be associated with increased GBD prevalence in diabetic patients included supersaturation of bile , Heuman et al. Changes in the cholesterol nucleation , Afdahl et al. Decrease motility of gall bladder , Joon Soo Hahm et al [. One study suggested that diabetic subjects secrete more lithogenic bile than non-diabetic subjects , Lausko et al ,and the rate of gallbladder emptying was delayed in subjects with autonomic neuropathy, Joon et al. Our results were in agreement with other studies Steven et al showed the prevalence of self-reported gall bladder disease was (34.2%) in diabetic women and (7.2%) in diabetic men . This study shows that the risk factors for GBD are the age , BMI , female gender and parity continue to be a risk factors for GBD even among diabetic patients with no significant differences between the two groups .

However diabetic female and the diabetic obese patients with BMI more than 25 kg/m^2 shows increased in frequency of GBD in comparison to non-diabetic subjects . The explanation my by that the obesity is associated with increased insulin resistance and hyperinsulinemia and positive association was reported between GBD and high insulin level . The GBD may be the result of the higher insulin concentration observed in diabetic patients who are obese in comparison to that of non-diabetic obese subjects . Similar results had been reported in other studies , Misciagna et al. Our study goes with one case-control study of clinical gallbladder disease in subjects , Steven et al, found that the female gender increased the risk of GBD more in diabetic patients than in non-diabetic subjects . Our study shows OHD therapy was associated with a mild increased the risk of GBD although this relation was not statistically significant . In contrast to the previous study, which showed that insulin therapy was associated with increased the risk of GBD . This study shows that the duration of diabetes was positively related to the prevalence of GBD . The relationship between duration of diabetes and GBD in the individuals with type two diabetes mellitus had been examined in two previous studies , one case-control study . In Lausko et al, study and no association was found . Other study , Steven et al. Found a positive association . This association could be the result of increased insulin resistance with duration of diabetes, or increased risk of autonomic neuropathy with duration of diabetes. Like Steven et al, study also found there was no relation between FBS levels and GBS in diabetic patients , but this could be a single FBS which was not a good measure for assessment of diabetes control. Finally , in contrast with previous reports. There is a positive relationship between the GBD and Hb A_{1C} level which indicate a poor glycemic control. These results were in agreement with a previous study, which showed that the gallbladder motility impairment and gallstones formation was significantly greater in comparison with the control and Hb A1C level in diabetes .

CONCLUSIONS

1. The frequency of GBD increases type two diabetes mellitus in two fold (32%) in comparison to that in the general population (15%) .
2. There is no significant difference in the effect of other risk factors of GBD like age , parity , and family history of GBD between diabetic and non-diabetic subjects .
3. There is significant increase in the frequency of GBD in diabetic obese patients and diabetic female patients in comparison with non-diabetic subjects who have the same weight and gender .
4. The frequency of GBD increases with increased duration of diabetes mellitus and Hb A_{1C} .
5. There is no association between FBS and frequency of GBD in diabetic patients .

RECOMMENDATION

From this study we advise to screen patients with for type two diabetes mellitus presence of GBD especially those with long duration of diabetes and high level of Hb A_{1C} in the blood .

TABLES AND FIGURES

Table 1: the prevalence of GBD in diabetic and non-diabetic subjects.

group	Total number	With GBD		P value
		no	%	
diabetic	200	64	%32	<0.05
Non-diabetic	200	30	%15	

frequency

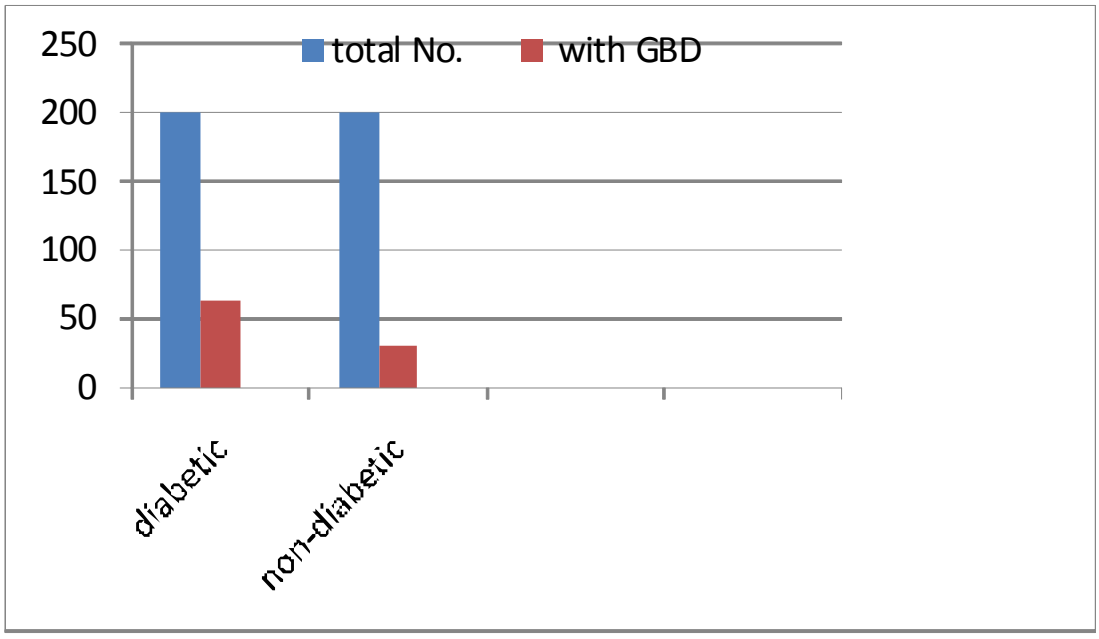

figure 1: the prevalence of GBD in diabetic and non-diabetic subjects.

Table 2: the relation between GBD and age in both diabetic and non-diabetic subjects

Percentage with GBD

Age group	diabetic			Non-diabetic			p value
	Total No.(200)	No. With GBD	% With GBD	Total No.(200)	No. With GBD	% With GBD	
30-39	20	-	-	62	2	3.6	>0.05
40-49	26	4	15.4	26	6	23.1	
50-59	48	14	29.2	42	4	9.5	
60-69	64	22	34.4	34	4	11.8	
70-79	30	16	53.3	34	10	29.4	
80-89	12	8	66.7	12	4	33.3	

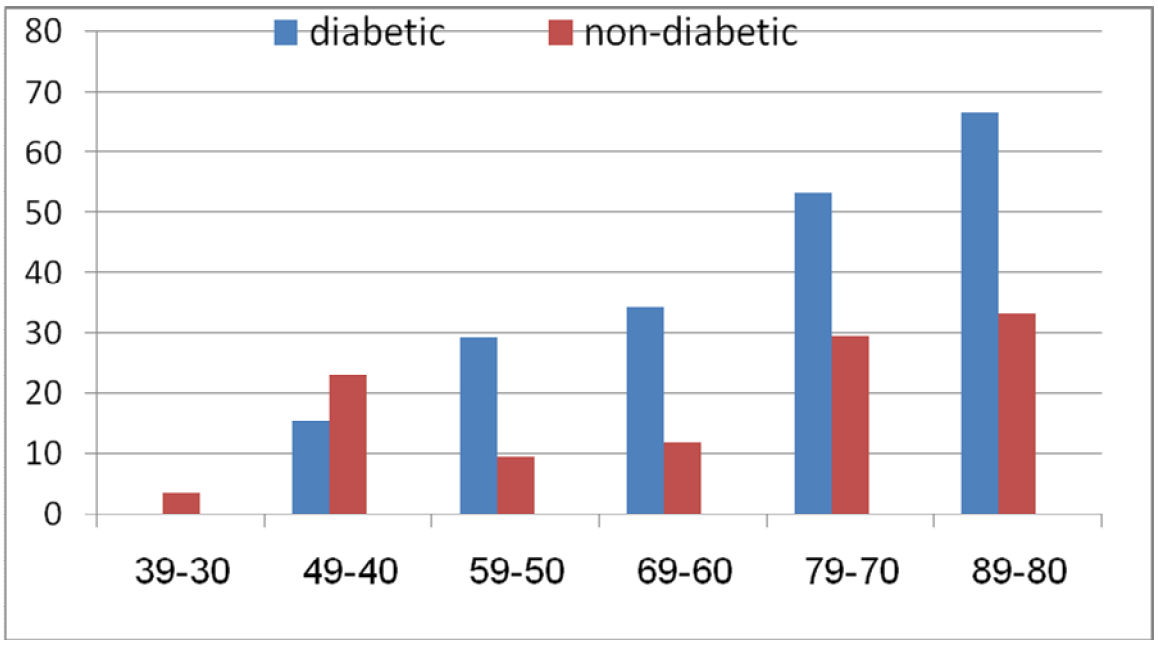

Figure2: : the relation between GBD and age in both diabetic and non-diabetic subjects

table3: : the relation between GBD and BMI in both diabetic and non-diabetic subjects.

BMI	diabetic			Non-diabetic			P value
	Total No.(200)	No. With GBD	% With GBD	Total No.(200	No. With GBD	% with GBD	
<20	12	-	-	10	2	20	-
٢٠_٢٤,٩	52	8	15.4	36	4	11.1	>0.05
٢٥-٢٩,٩	86	28	32.6	88	10	11.4	<0.02
≥٣٠	50	28	56	66	14	21.2	<0.01

Percentage with GBD

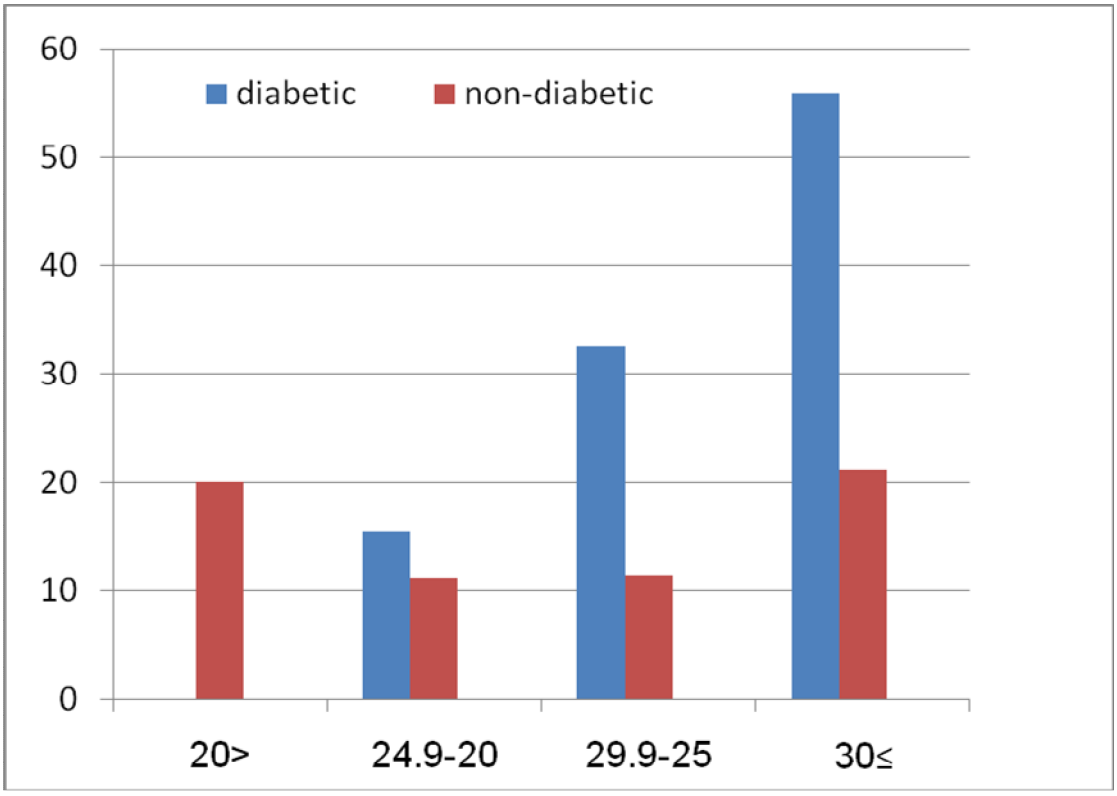

Figure 3: : the relation between GBD and BMI in both diabetic and non-diabetic subjects.

Table4 : : the relation between GBD and family history in both diabetic and non-diabetic subjects.

Family history	diabetic			Non-diabetic			P value
	Total No.(200)	No. With GBD	% With GBD	Total No.(200)	No. With GBD	% With GBD	
positive	38	22	57.9	26	10	38.5	>0.05
negative	162	42	25.9	174	20	11.5	>0.05

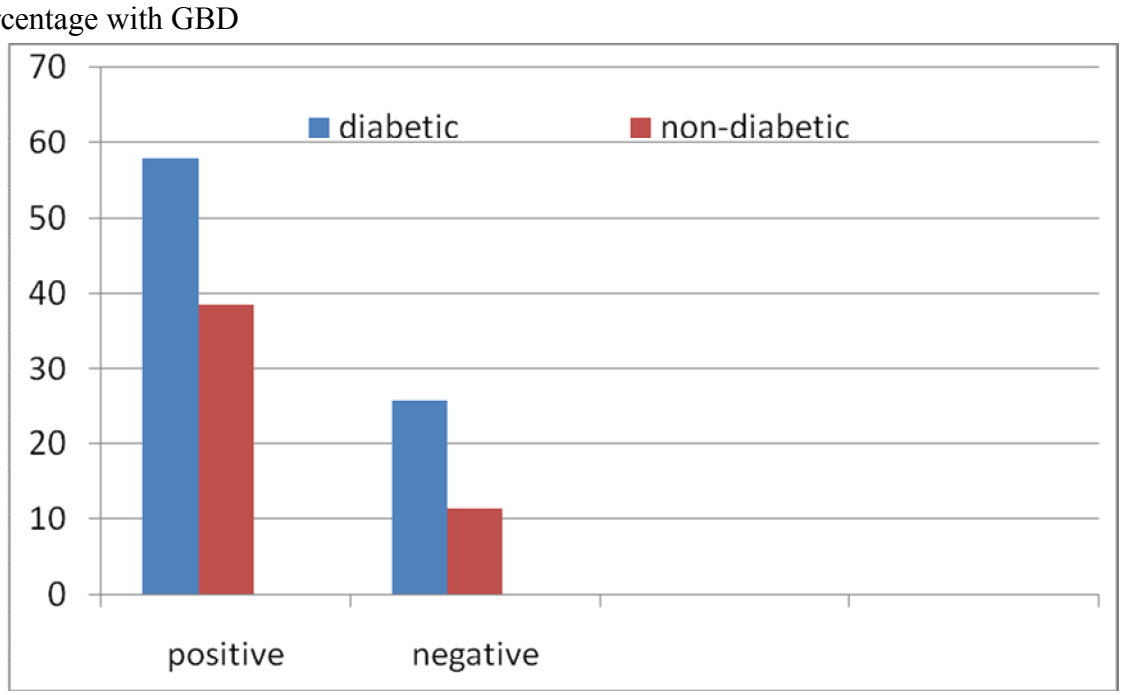

Figure 4 : : the relation between GBD and family history in both diabetic and non-diabetic subjects.

Table5: : the relation between GBD and sex in both diabetic and non-diabetic subjects.

sex	diabetic			Non-diabetic			P value
	Total No.(200)	No. With GBD	% With GBD	Total No.(200)	No. With GBD	% With GBD	
female	116	42	36.2	120	16	13.3	<0.04
male	84	22	26.2	80	14	17.5	>0.05

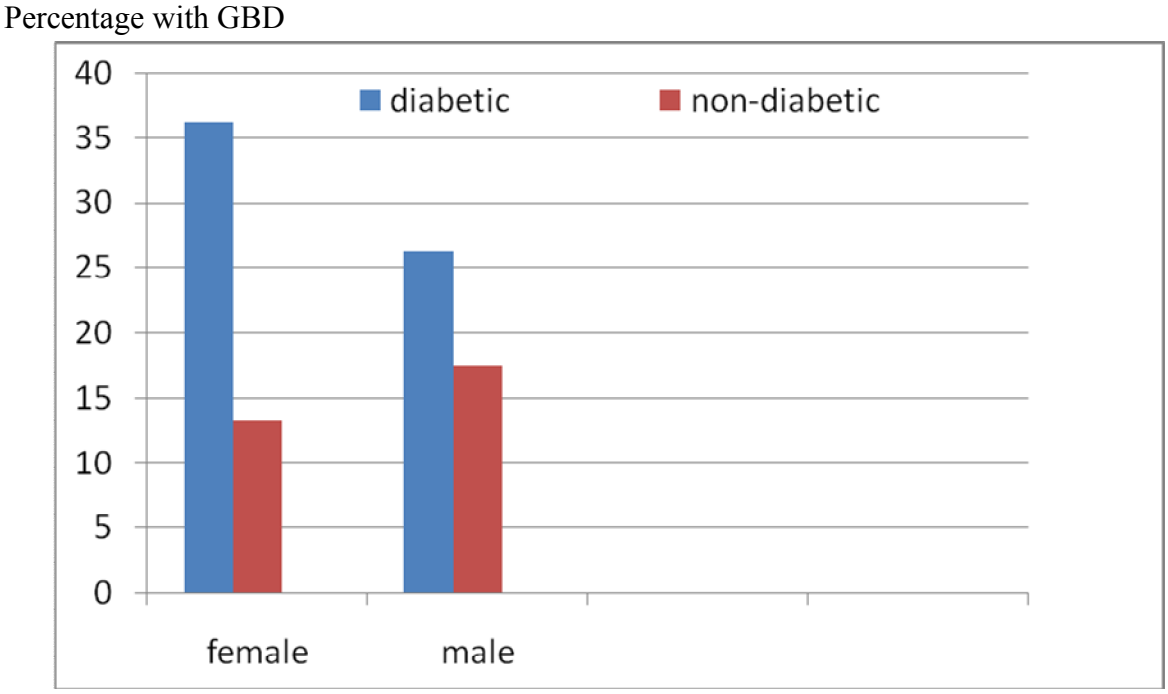

Figure5: : the relation between GBD and sex in both diabetic and non-diabetic subjects.

Table 6: the relation between GBD and parity in female in both diabetic and non-diabetic subjects.

parity	diabetic			Non-diabetic			P value
	Total No.(116)	No. With GBD	% With GBD	Total No.(120)	No. With GBD	% With GBD	
≤3	38	10	23.7	26	2	6.5	>0.05
>3	78	28	38.7	94	14	20.6	>0.05

Percentage with GBD

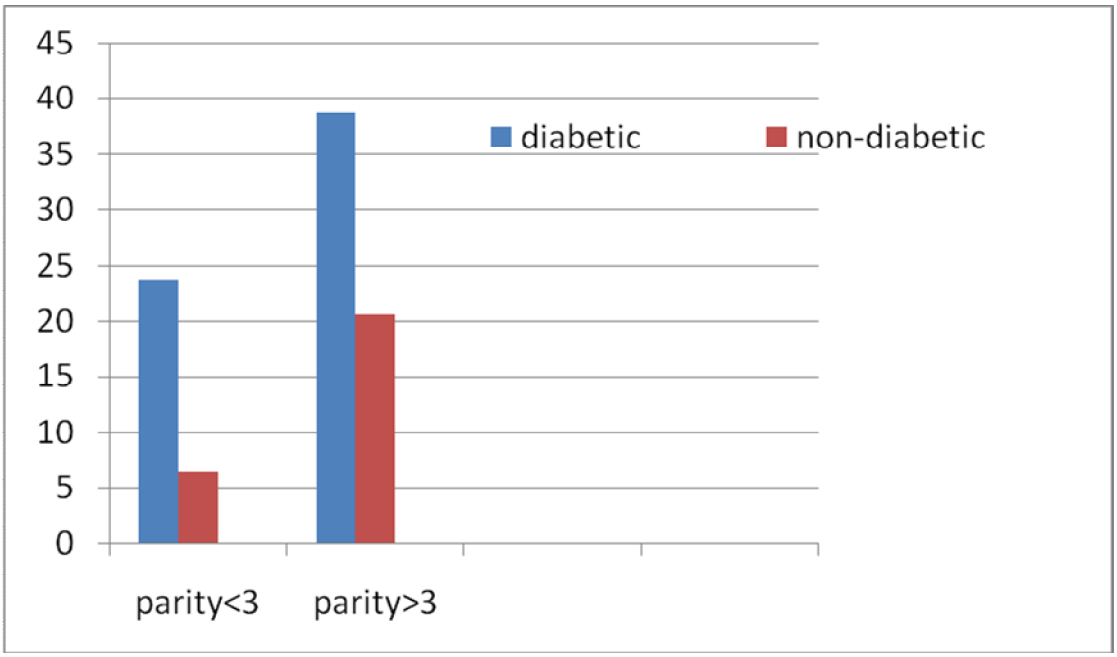

Figure 6: the relation between GBD and parity in female in both diabetic and non-diabetic subjects.

Table 7: the relation between GBD and duration of diabetes mellitus in diabetic subjects.

Duration of DM(years)	Diabetic with GBD		Diabetic without GBD		P value
	No.(64)	%	No.(136)	%	
<5	12	18.7	28	20.6	<0.05
5-10	20	31.2	60	44.1	
>10	32	50	48	25.3	

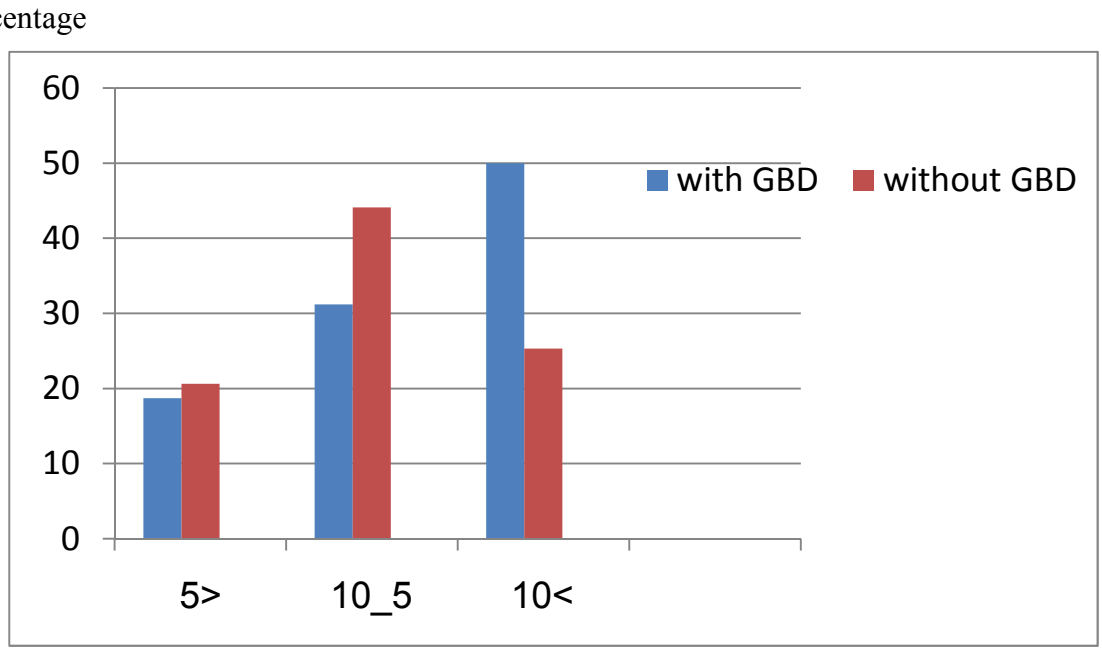

Figure 7: the relation between GBD and duration of diabetes mellitus in diabetic subjects.

Table 8 : the relation between GBD and type of therapy in diabetic subjects.

therapy	Diabetic with GBD		Diabetic without GBD		P- value
	No.(64)	%	No.(136)	%	
insulin	18	23.7	58	76.3	>0.05
OHD	46	37.1	78	62.9	

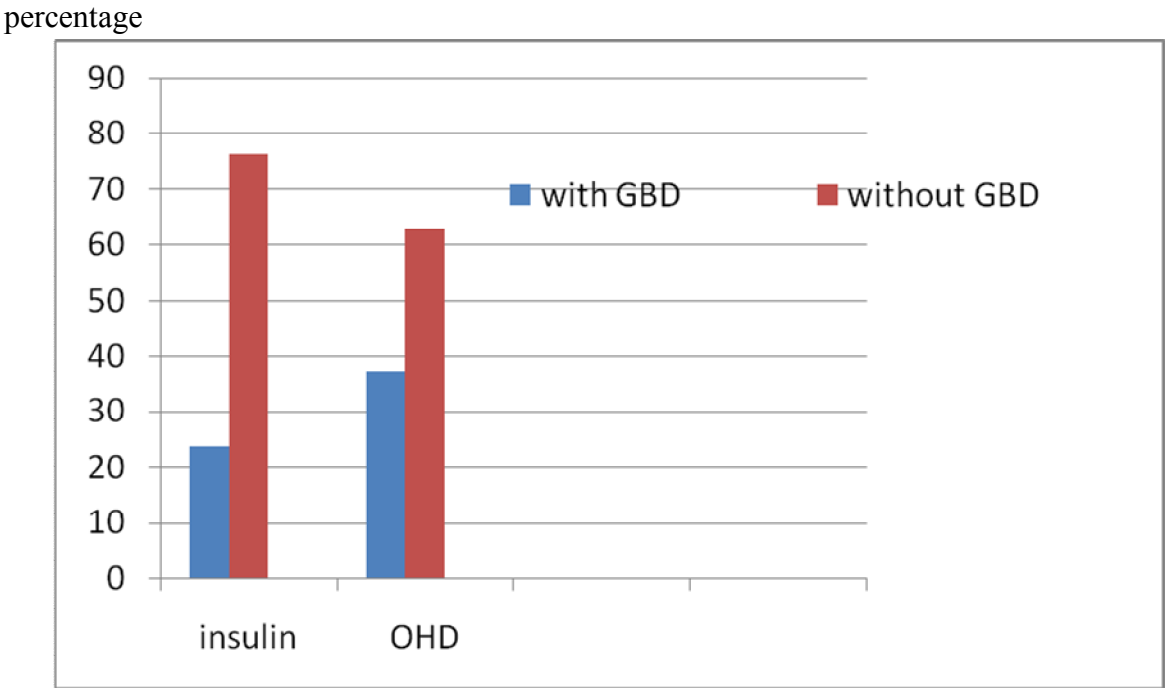

Figure 8 : the relation between GBD and type of therapy in diabetic subjects.

Table 9: the relation between the haemoglobin A 1c and GBD in diabetic subjects.

Hb A1c level	Diabetic with GBD		Diabetic without GBD		p-value
	No.(64)	%	No.(136)	%	
<6	2	3.1	18	13.2	<0.03
6-	12	10.8	24	25.6	
7-	4	14.3	30	14.1	
8-	18	28.1	32	23.5	
9-	10	15.6	22	16.2	
10-	18	28.1	10	7.4	

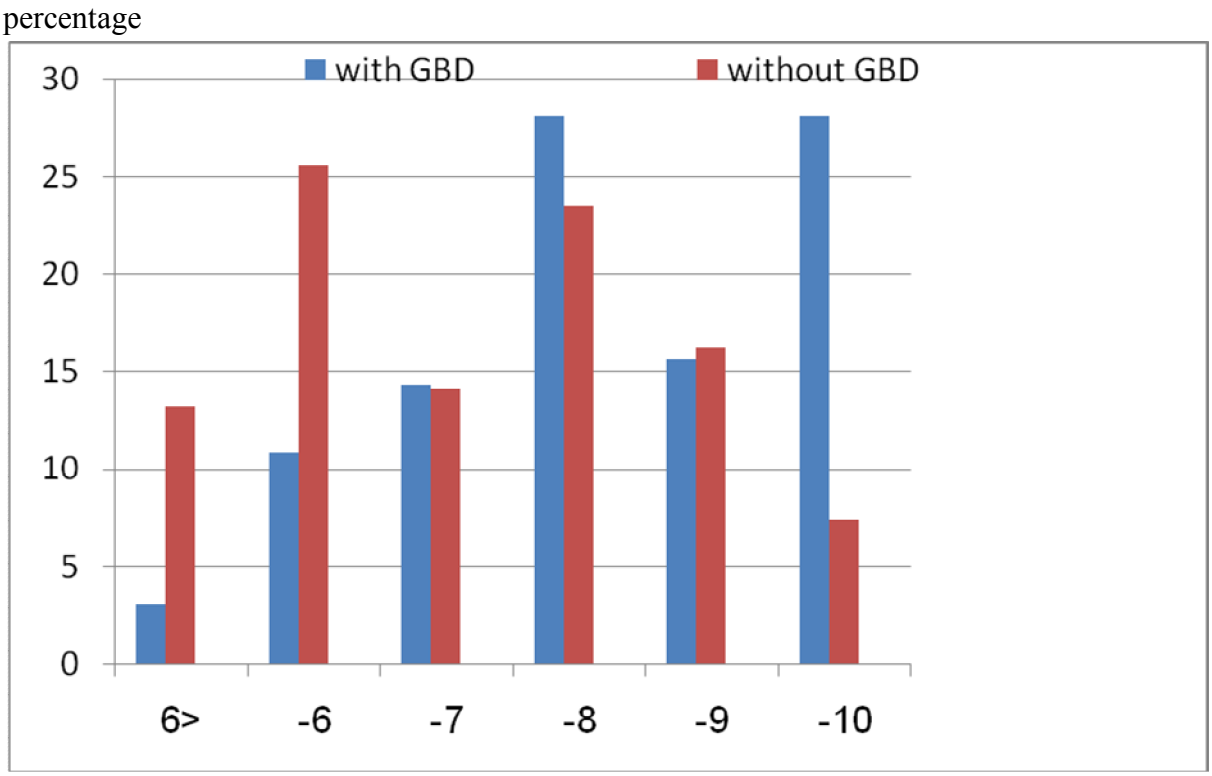

Figure 9: the relation between the haemoglobin A 1c and GBD in diabetic subjects.

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