

## Research

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# Acute Variceal Bleeding in Patients with Liver Cirrhosis with and without Diabetes

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### ABSTRACT

**Objectives:** To study the effect of diabetes mellitus on presentations, course, and outcome of acute variceal bleeding in cirrhotic patients.

**Methods:** We compared 2 matched groups of patients, a diabetic group and non-diabetic group, where all of the patients presented with acute esophageal varices due to liver cirrhosis. All patients underwent history taking, clinical examination, emergency treatment, upper endoscopy, laboratory investigations and abdominal ultrasound; they followed up until hospital discharge.

**Results:** The diabetic group showed statistically significant unstable course in 73.3% of them compared to 36.6% in the control; more attacks of melena ( $2.2 \pm 1.03$ ) compared to control ( $1.7 \pm 0.88$ ), and also had significantly disturbed level of consciousness compared to control (36.7% versus 10% respectively); moreover they have significantly more right and left lobe enlargement than control (70% versus 26.7%, and 66.7 versus 40% respectively), significantly more echogenic liver (70% versus 33.3), highly significant more portal vein dilatations (73.3% versus 16.7%) and highly significant more collaterals (50% versus 23.3%); the splenic size was also significantly more enlarged in diabetics (60%) than control (40%), and the splenic vein diameter was significantly more dilated in diabetics (33.3%) versus control group (6.7%); finally the mortality was more in the diabetic group.

**Conclusions:** Diabetic patients with acute variceal bleeding may show more morbidity and mortality rates.

**KEYWORDS:** Diabetes; Esophageal varices; Liver cirrhosis.

### INTRODUCTION

Variceal bleeding is one of the major complications of portal hypertension; Gastro-esophageal varices are present in 40-60% of patients with cirrhosis and their rupture constitutes the most common lethal cause of mortality in those patients. It is associated with a mortality of at least 20% at 6 weeks despite improvements in therapy,<sup>1-3</sup> and the 1-year recurrence rate of variceal bleeding is 60% if no preventive treatment is given.<sup>4</sup> However, it has decreased from 47% to 13% with the use of pharmacological, endoscopic, and radiological intervention.<sup>5,6</sup> The presence of esophageal varices correlates with the severity of liver disease as it is found in about 40% of Child A, and 85% of Child C patients.<sup>7</sup> Various factors have been proposed as predictors of outcome of variceal bleed such as age of the patient, gender, stage of cirrhosis, etiology of the disease, associated conditions like renal failure, Hepatocellular carcinoma (HCC), and Diabetes Mellitus (DM) which is frequently associated with cirrhosis.<sup>8</sup> Regardless the cause for diabetes, hyperglycemia induces splanchnic hyperemia, increases portal pressure and may increase the risk of variceal bleeding.<sup>9</sup> Moreover, the higher mortality rate in patients

with diabetes is not only due to the complications of DM but also due to increased risk of hepatocellular failure in long-term follow up.<sup>10</sup> In our country, both variceal bleeding due to cirrhosis and diabetes mellitus are common causes of morbidity and mortality which warrants an in-depth study of such relationship.

## OBJECTIVES

To study the effects of diabetes mellitus on presentation, course, and mortality of acute variceal bleeding in cirrhotic patients.

## METHODS

### Study Type

This is a prospective case-control study which was carried out at the Internal Medicine Department and Gastroenterology Endoscopic Unit of Suez Canal University Hospital, Egypt. The study conformed to the Declaration of Helsinki for Human Rights and was approved by the University's Research Ethics Committee.

### Patients

Sixty cirrhotic patients (who met the inclusion criteria) with acute variceal bleeding with or without DM were included in the study. The patients were divided into two groups which were matched for age and gender: Group 1 (diabetic group, who were labelled as diabetics based on their history regardless of the cause of diabetes), included 30 consecutive cirrhotic patients with variceal bleeding and had a history of DM, and Group 2 (control group) which included 30 cirrhotic patients with variceal bleeding and had no history of DM. All patients were recruited prospectively at the time of admission during the period from October 2013- June 2014 after screening of 287 patients.

### Inclusion Criteria

Adult patients aged  $\geq 18$  years, both sexes, with liver cirrhosis and variceal bleeding with or without DM, patient's gave written informed consent and including the adherence.

### Exclusion Criteria

Severely decompensated patients as those with HCC with bleeding, patients in hepatic encephalopathy, non variceal bleeding, and patients' refusal to participate in the study.

### Study Procedure

During the hospital stay all patients were formally clerked with complete history taking, clinical assessment; laboratory investigations including Complete Blood Count (CBC), Liver function tests (ALT, AST, S. albumin, S. bilirubin and al-

kaline phosphates), renal function tests (S. creatinine, B. urea), fasting blood sugar, and 2 h post-prandial; also abdominal Ultrasound (US) were done for all the patients. Cirrhosis and portal hypertension were diagnosed on the basis of clinical, biochemical, virological data and imaging scanning; other data including age, gender, Child-Pugh class, site of varices and etiology of cirrhosis was recorded. Source of upper gastrointestinal bleed was confirmed by upper gastrointestinal endoscopy. Esophageal varices were graded from I-IV.<sup>11</sup> Gastric varices were classified as described by Sarin and Kumar in 1989;<sup>12</sup> the source of bleeding was identified as variceal if there was active bleeding from a varix or there were signs of recent bleeding from a varix, or there was a single varix without any other potential source of bleeding. Failure to control bleed was defined according to the Baveno III consensus report<sup>13</sup> as the occurrence of hematemesis and reduction in blood pressure of more than 20 mmHg and/or transfusion of 2 units of blood or more (over and above previous transfusions) required to keep the haemoglobin above 9 g/dL, or a drop in haemoglobin of 2 g/dL within first 24 hours of control of bleeding. The preferred therapeutic modality used was Endoscopic Variceal Ligation (EVL) with Six Shooter Saeed multi band ligation. In some patients with massive bleeding, variceal sclerotherapy with Ethanolamine Oleate was performed. Gastric varices were injected with n-butyl cyanoacrylate. No therapeutic intervention was done for patients with portal gastropathy. Somatosatin is given as 2 ampules in 500 cc glucose 5%/8 h (if the patient was not diabetic) and 2 ampules + 500 cc glucose 5% + 4 I.U regular insulin /8 h (if the patient was diabetic). Other emergency protocols in our hospital were performed until the patient became haemodynamically stable when upper endoscopy was performed; the patient was prepared by Midazolam (10 mg IV or Diazepam 5 mg IV bolus until the patient was sedated, then a mouth piece was placed and upper GI endoscopy was introduced under complete visualization, the esophagus was assessed for presence of bleeding and managed according to the guidelines by band ligation or sclerotherapy with Ethanolamine Oleate, and/or Histocryl amp (Enbucrilat 0.5 gm) in cases with fundal varices. The patient also received antibiotic, in the form of ciprofloxacin 500 mg/12 h for 5 days, PPI (Omeprazole 20 mg /12 h for 7 days), and  $\beta$ -blocker "propranolol" was given 20-240 mg/d guided by heart rate. Other causes of variceal re-bleeding as Thrombocytopenia and coagulopathy were corrected by platelet or Fresh Frozen Plasma (FFP) transfusion, if needed. Then the patient was followed up as an in-patient for at least another 2 days until melena stopped (enema was clear) and haemodynamic stable was then discharged to be followed up in out-patient sessions of upper gastrointestinal endoscopy.

### Measurement criteria for the course and outcome

As every patient had his different course pattern, we simply defined them as having stable course or unstable course. Patients were identified as having unstable course if they developed hepatic encephalopathy, spontaneous bacterial peritonitis, upper gastrointestinal re-bleeding after the initial endoscopic

treatment and/or renal impairment during the hospital stay. The death rate was also recorded in terms of mortality.

#### Data management and statistical analysis

Data collected throughout the history, basic clinical examination, laboratory investigation, and imaging results were coded, entered and analyzed using Microsoft Excel software. The data was then imported into (SPSS 13.0) software for analysis. According to the type of data the following tests were used to test differences for significance; Chi-squared and Fisher exact test, for categorical data and Student's *t*-test for continuous data. Multivariate logistic regression analysis was used to analyze the different studied variables. Continuous data were presented as the mean±SD unless otherwise specified. Categorical data were presented as numbers and percentages. P value was set at <0.05 for significant results.

#### RESULTS

There were no any statistical significant differences between the 2 groups, Table 1 shows that the mean age of the diabetic group was 53.8±10.5 compared to 52.1±11.9 in the control group; the males constitute 60% of the diabetic group, compared to 80% in the control; most of the patients live in rural areas in the diabetic and control groups (63.3%, and 76.6% respectively), and the majority of the patients were identically married (96.7%) in both groups. With regards to the status of hepatic diseases in both groups Table 2 shows that there were no significant statistical differences in both group as regard to the presence of cirrhosis, the etiology and the functional status of the liver. However, most of the diabetic group showed statistically significant unstable course in 73.3% of them compared to 36.6% in the control; moreover, the frequency of hospitals admission in the diabetics were more significant than the control (1.6 *versus* 0.7 respectively); moreover, the mortality rate was significantly higher among the diabetes. With regards the clinical manifestations, it was shown in Table 3 that diabetics have significantly more attacks of melena (2.2±1.03) compared to the control group (1.7±0.88), and also had significantly disturbed level of consciousness compared to the control group (36.7% *versus* 10% respectively). Regarding the laboratory investiga-

tions, Table 4 shows that there were no statistical significant differences for CBC, liver functions or renal functions. With regards to abdominal ultrasound evaluation in both groups Table 5 shows that diabetics had significantly more right and left lobe enlargement than control (70% *versus* 26.7%, and 66.7 *versus* 40% respectively), significantly more echogenic liver (70% *versus* 33.3), highly significant more portal vein dilatations (73.3% *versus* 16.7%) and highly significant more collaterals (50% *versus* 23.3%); the splenic size was also significantly more enlarged in diabetics (60%) than control (40%), and the splenic vein diameter was significantly more dilated in diabetics (33.3%) *versus* control group (6.7%). Finally, there was no significant difference as regard to the presence of ascites in both groups.

#### DISCUSSION

Both diabetes and liver cirrhosis are common health problems in Egypt; their presence in the same patient means a double pathological insult for the liver, which increases morbidity and mortality, regardless of the initial etiology and the cause of liver cirrhosis. This research attempted to explore how diabetic patients with acute variceal bleeding differ from those who are not diabetics. We included 2 matched groups for age and gender, a diabetic group and a control group; although we did not match for the etiology of liver cirrhosis, the majority of patients in both group have chronic HCV infection, this is mostly because HCV is the leading cause of chronic liver diseases and cirrhosis in Egypt,<sup>14</sup> and there were no differences in both group in terms of the functional status of the liver as most of them were compensated functionally. However, the diabetic group experienced significantly more unstable course for their liver diseases in their past history compared to the control, and more hospital admissions which may be attributed to their double burden. As regards the clinical manifestations at the time of admission there were no statistically significant differences, but during the hospital course the diabetic patients had significantly more attacks of upper gastrointestinal bleeding compared to control; this may be explained that they have more degree of portal hypertension as a result of the hyperglycemia and the insulin resistance,<sup>8,15</sup> or to what more recently discovered in experimental animals that Diabetes Diminishes the Portal-Systemic Collateral Vascular Response to Vasopressin *via* Vasopressin Receptor and *Gα* Pro-

Age (years)	Mean ± SD	Diabetic (n=30)		Control (n=30)		Used test	p-value
	Range	53.8	10.5	52.1	11.9		
Gender (%)	Male	18	60.0	24	80.0	$\chi^2=2.86$	0.09
	Female	12	40.0	6	20.0		
Residence (%)	Urban	11	36.7	7	23.3	$\chi^2=1.27$	0.26
	Rural	19	63.3	23	76.7		
Marital status (%)	Single	1	3.3	1	3.3	Fisher exact	1.00
	Married	29	96.7	29	96.7		

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 1: Demographic data of both studied groups.

		Diabetic (n=30)		Control (n=30)		Used test	p-value
Pathology (%)	Cirrhosis	29	96.7	30	100.0	Fisher exact	0.50
	Cirrhosis & HCC	1	3.3	0	0.0		
Etiology (%)	HCV	26	86.7	28	93.3	Fisher exact	0.67
	HCV & HBV	4	13.3	2	6.7		
Functional (%)	Compensated	25	83.3	24	80.0	$\chi^2=0.11$	0.74
	Decompensated	5	16.7	6	20.0		
Course (%)	Unstable	22	73.3	11	36.6	$\chi^2=8.2$	0.004**
	Stable	8	26.7	19	63.3		
Re-bleeding (%)		14	46.4	3	10	Fisher exact	0.003**
Encephalopathy (%)		11	36.6	3	10	Fisher exact	0.03*
Spontaneous Bacterial Peritonitis (%)		8	26.6	1	3.3	Fisher exact	0.0138*
Renal impairment (%)		3	10	1	3.3	Fisher exact	0.61
Duration of CLD (years)	Mean $\pm$ SD	25.5	14.4	24.5	13.7	0.28	0.78
Admission before (times)	Mean $\pm$ SD	1.60	0.4	1.3	0.7	2.2	0.046*
mortality		5	16.6	2	6.7	Fisher exact	0.26

\*Significant p-value &lt;0.05

Table 2: Mortality, hospital course and the status of hepatic disease of both studied groups.

		Diabetic (n=30)		Control (n=30)		Used test	p-value
Jaundice (%)	Yes	3	10.0	4	13.3	Fisher exact	1.00
	No	27	90.0	26	86.7		
Melena (%)	Yes	29	96.7	26	86.7	Fisher exact	0.35
	No	1	3.3	4	13.3		
No. of attacks	Mean $\pm$ SD	2.2	1.03	1.7	0.88	2.01	0.041*
Fresh bleeding per rectum (%)	Yes	1	3.3	0	0.0	Fisher exact	0.50
	No	29	96.7	30	100.0		
Spider nevi (%)	Yes	7	23.3	4	13.3	$\chi^2=1.0$	0.32
	No	23	76.7	26	86.7		
Tremors (coarse) (%)	Yes	4	13.3	1	3.3	Fisher exact	0.35
	No	26	86.7	29	96.7		
Palmer Erythema (%)	Yes	7	23.3	8	26.7	$\chi^2=0.09$	0.76
	No	23	76.7	22	73.3		
Lower limb edema (%)	Yes	1	3.3	0	0.0	Fisher exact	0.50
	No	29	96.7	30	100.0		
Consciousness level (%)	Conscious	19	63.3	27	90.0	$\chi^2=5.96$	0.015*
	Disturbed	11	36.7	3	10.0		
Suprapubic hair (%)	Normal	17	56.7	16	53.3	$\chi^2=0.07$	0.79
	Abnormal	13	43.3	14	46.7		
Gynecomastia (male n=42) (%)	Yes	14	77.8	16	66.7	$\chi^2=0.27$	0.60
	No	4	22.2	8	33.3		
Nutritional status (%)	Good	5	16.7	10	33.3	$\chi^2=2.22$	0.14
	Fair	22	73.3	18	60.0		
	Poor	3	10.0	2	6.7		

\*Significant p-value &lt;0.05, \*\*highly significant p-value &lt;0.01

Table 3: Clinical manifestations of the studied patients of both studied groups.

	Diabetic (n=30)		Control (n=30)		t-test	p-value
	Mean (SD)		Mean (SD)			
Hb	9.02	2.2	8.7	2.5	0.417	0.680
Platelet count	144.8	89.7	133.3	56.8	0.540	0.593
Total serum bilirubin	1.47	0.96	1.6	0.9	0.337	0.738
ALT	52.5	37.8	55.9	65.02	0.233	0.817
AST	71.3	85.2	69.8	101.2	0.058	0.954
Albumin	3.057	0.43	2.96	0.57	0.767	0.449
Alkaline Phosphatase	33.7	9.59	31.1	7.9	1.445	0.159
S. creatinine	1.18	0.59	0.9	0.25	1.057	0.299
B. urea	63.5	45.6	51.8	26.9	1.130	0.268
PT	16.34	3.42	16.3	3.01	0.004	0.997
INR	1.399	0.48	1.3	0.43	1.064	0.296
FBS	150.9	66.7	80.9	13.7	5.350	<0.0001**
PPS	238.4	108.6	115.8	9.01	6.078	<0.0001**

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 4: Laboratory investigations of both studied groups.

		Diabetic (n=30)		Control (n=30)		$\chi^2$ test	p-value
		No.	%	No.	%		
Right lobe	Normal	8	26.7	18	60.0	$\chi^2=9.5$	0.002**
	Enlarged	21	70.0	8	26.7		
	Shrunken	1	3.3	4	13.3		
Left lobe	Normal	10	33.3	18	60.0	$\chi^2=4.3$	0.038*
	Enlarged	20	66.7	12	40.0		
Echogenicity	Echogenic	9	30.0	20	66.7	$\chi^2=8.1$	0.004**
	Bright (fatty) liver	21	70.0	10	33.3		
Portal vein	Normal	8	26.7	25	83.3	$\chi^2=19.5$	<0.0001**
	Dilated	22	73.3	5	16.7		
Collaterals	Yes	15	50.0	7	23.3	$\chi^2=15.6$	<0.0001*
	No	15	50.0	23	76.7		
Spleen size	Normal	12	40.0	18	60.0	$\chi^2=4.6$	0.032*
	Enlarged	18	60.0	12	40.0		
Splenic vein diameter	Normal	20	66.7	28	93.3	$\chi^2=6.7$	0.0098**
	Dilated	10	33.3	2	6.7		
Ascites	Absent	27	90.0	26	86.7	Fisher exact	0.99
	Mild /moderate	3	10.0	4	13.3		

\*Significant p-value <0.05, \*\*highly significant p-value <0.01

Table 5: Abdominal ultrasound evaluation of the studied patients.

teins Regulations;<sup>16</sup> the presence of diabetes itself, is a risk factor to control variceal bleeding.<sup>17</sup> However, the hypothesis that the veins themselves may be directly affected by the diabetes as a part of the vasculopathy<sup>18</sup> need to be tested. In our study, diabetics also showed more significantly impaired consciousness level compared to control which may be attributed to the more attacks and more blood loss which may increase the degree of their encephalopathy.<sup>19</sup> As regards the laboratory investigations at the time of admission, there were no significant differences, apart from the blood sugar; even the liver enzymes in both groups were nearly identical, although a recently published mega trial

concluded that serum ALT concentrations were independently associated with type 2 diabetes in both sexes.<sup>20</sup> Contrary of the clinical presentation and laboratory investigations in our study, the ultrasound showed that the diabetics are significantly morphologically different from the control group; they have more hepatomegaly and splenomegaly, increased portal pressures with more dilated portal veins and more collaterals. In addition, their livers appeared more fatty and bright; this raised the hypothesis that these morphological differences may be attributed to diabetes alone as it is the only variable between the 2 groups. Based on our knowledge and previous studies we can

understand the presence of bright fatty liver and hepatomegaly in the diabetics;<sup>21,22</sup> we can also partially explain the presence of collaterals and portal veins dilatation;<sup>23,24</sup> but all of these were not reflected on the laboratory investigations or the clinical presentations except the increased frequency of bleeding; even the presence of ascites were comparable in both groups which may be due to the comparable levels of serum albumin that could not be overcome by the degree of portal hypertension in diabetics. However, the limitation of this study is relatively small sample size, and the results of the study should be addressed and re-evaluated on larger groups.

## CONCLUSION

Patients with acute variceal bleeding due to liver cirrhosis and diabetes are mostly presenting with more evidence of portal hypertension, more attacks of bleeding and less responsiveness to pharmacological treatments.

## ETHICAL CONSIDERATIONS

This study was approved by the University's Research Ethical Committee and an informed consent was taken from all the participants prior to recruitment into the study.

## CONFLICTS OF INTEREST

We have not any conflict of interest to declare.

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