Diabetes Mellitus and Spontaneous Bacterial Peritonitis in Cirrhosis - Association or Coincidence?

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ABSTRACT

BACKGROUND

Spontaneous bacterial peritonitis (SBP) is frequent, clinically significant and infection associated with frequent complications in cirrhotic patients. Diabetes mellitus (DM) and cirrhosis are prone to infections, increased incidence of infections in combined scenarios need further evaluation. Type 2 diabetes mellitus in patients with liver cirrhosis is five times higher than in the general population. Some studies showed that in patients with liver cirrhosis, DM has been associated with a higher risk for hepatic decompensation, encephalopathy, kidney injury and higher overall mortality. But other studies showed no increase in the incidence of SBP in the diabetic patient with cirrhosis. There is no data regarding the frequency of SBP, a comparison of SBP among diabetics and non-diabetics is available in this region of South India. The objectives of the study were to determine the average frequency of spontaneous bacterial peritonitis (SBP) among patients with diabetes mellitus and non-diabetic mellitus in cirrhosis and compare the frequency of SBP in diabetics and non-diabetics with cirrhosis.

METHODS

This is a retrospective cross-sectional study conducted in the Department of Gastroenterology, Pushpagiri Institute of medical sciences and research centre, Thiruvalla, from January 2017 to January 2019. The study included consecutive 104 patients out of 194 patients (26 missed for follow up and 64 were repeated admissions). All were in regular follow up (at least once in 12 months), irrespective of antibiotic prophylaxis. Those who missed follow up for more than 12 months were excluded from the study. All variables were ordinal or nominal, statistical calculation was done by using percentages and proportions, chi-square test was used for calculation of the significance in comparison of frequency SBP between diabetics and non-diabetics and p-value < 0.05 taken as significant.

RESULTS

The study included 104 SBP patients after the exclusion, in which 64 patients were diagnosed with DM as per the guidelines. The overall prevalence of DM and non DM among SBP patients in the present study was found to be 61.5 % and 38.5 % respectively. In diabetic patients, 20 patients had SBP once, 40 patients had two times and 4 patients had 3 times during the study period. It contributed around 31 % with once, 62 % with twice and 6 % with thrice SBP during the study period. The average frequency of SBP and variants was found to be 1.7 (diabetic-1.81, Non-diabetic-1.4) during the study period of 2 years. Comparison of frequency of SBP in diabetics and non-diabetics, p-value was found to be 0.003.

CONCLUSIONS

Spontaneous bacterial peritonitis frequency is significantly increased in diabetic patients in comparison with non-diabetics in cirrhosis.

KEY WORDS

SBP: Spontaneous Bacterial Peritonitis, DM: Diabetes Mellitus, Cirrhosis.

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BACKGROUND

Patients with liver cirrhosis have a higher susceptibility to infections.[1] SBP (spontaneous bacterial peritonitis) is considered to be frequent, clinically significant and infection associated with complications in cirrhotic patients. Antibiotic treatment is becoming more and more challenging due to the emergence of multidrug-resistant bacteria, mostly in hospitalised patients.[2-4] It is one of the most common comorbidities in type 2 diabetes mellitus (DM) affecting 20–40 % of cirrhotic patients.[5-7] Type 2 diabetes mellitus in patients with liver cirrhosis is five times higher than in the general population.[6] Diabetes is known to increase the risk for bacterial infections in the general population.[8,9] In patients with liver cirrhosis, DM has been associated with a higher risk for hepatic decompensation, encephalopathy, kidney injury and higher overall mortality.[10,11] Presence of DM is associated with a more complicated course of cirrhosis and a higher likelihood for hepatic decompensation.[11,12] HD is more likely to be negatively affected by the underlying hepatic disease and its complications than by HD itself.

SBP manifested in significantly higher diabetic patients and frequency was found to be 2-3 times over 2 to 3 years.[13-15] Li Zhang et al. reported, the patients with hepatocirrhosis ascites complicated with diabetes showed older age, longer hospitalization time, more SBP and more ascites; diabetes mellitus, times of ascites, hospitalization days and TBIL increased the risk of SBP in hepatocirrhosis ascites.[15] Another study by Lars Bossen et al. stated that the risk of infections was the same in patients with cirrhosis, ascites and diabetes as in patients with cirrhosis and ascites alone. Thus, their combined effects do not exceed the effect of cirrhosis alone. There are other research papers that also concluded that DM does not affect the development of SBP in cirrhotics.[15-16] A study by Nick Wlazlo et al. stated the presence of DM at baseline in patients with cirrhosis as associated with an increased risk of SBP, which may represent an increased susceptibility to infections but it's not independently associated with mortality.[16]

The study population included patients with DM and non-DM; frequency of the SBP was compared between these two groups. There is no data regarding the frequency of SBP, a comparison of SBP among diabetic and non-diabetics is available in this region of South India.

Objectives

1. To determine the average frequency of spontaneous bacterial peritonitis (SBP) among patients with diabetes mellitus and non-diabetic mellitus in cirrhosis.
2. To compare the frequency of SBP in diabetics and non-diabetics with cirrhosis.

METHODS

This is a retrospective cross-sectional study conducted in the Department of Gastroenterology, Pushpagiri Institute of medical sciences and research centre, Thiruvalla, Kerala, India from January 2017 to January 2019.

The study included consecutive 104 patients admitted with a diagnosis of SBP. All were in regular follow up (at least once in 12 months) irrespective of antibiotic prophylaxis. Those who missed follow up for more than 12 months were excluded from the study. SBP and variants were diagnosed by ascitic fluid PMN count > 250 cells, culture positivity or both.[17] Diabetes mellitus is diagnosed as per ADA guidelines, by using fasting blood sugar, post prandial blood sugar, HbA1C.[18] All variables are nominal or ordinal, statistical calculation was done by calculating percentages and proportions, chi-square test was used for comparing the frequency of SBP among diabetic and non-diabetics and p-value < 0.05 was taken as significant. (Table no:1)

DM diagnosed as per ADA guidelines-

1. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.* OR
2. 2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* OR
3. HbA1c (glycosylated haemoglobin) ≥ 6.5 % (48 mmol/mol). OR
4. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

DCCT: Diabetes Control and Complications Trial, FPG: fasting plasma glucose, OGTT: oral glucose tolerance test, WHO: World Health Organization, 2-h PG, 2-h plasma glucose.

*In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

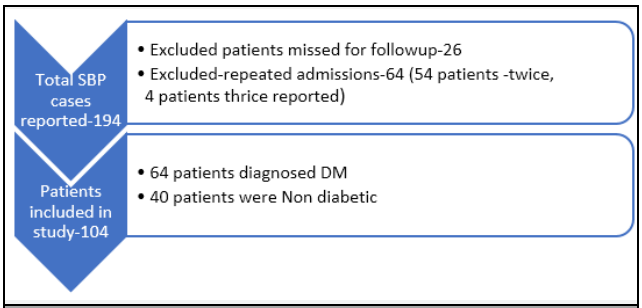

Figure 1. Methodology

RESULTS

Out of 104 patients in this study, 64 were diagnosed with DM as per the guidelines.[17] The overall prevalence of DM and non DM among SBP patients in the present study was found to be 61.5 % and 38.5 % respectively.

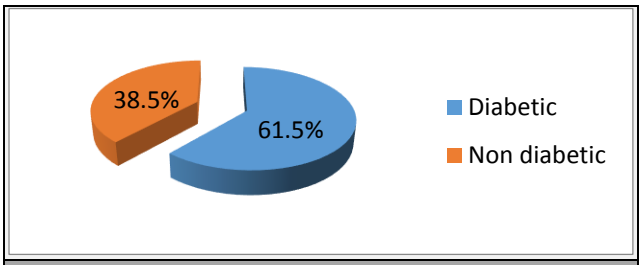

Figure 2. SBP with DM and without DM

In diabetic patients, 20 patients had SBP once, 40 patients had two times and 4 patients had 3 times during the study period. No patient was diagnosed more than three times during the study period. It contributed around 31 % with once, 62 % with twice and 6 % with thrice during the study period.

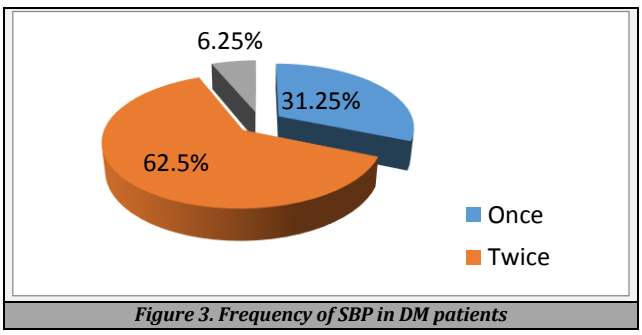

Figure 3. Frequency of SBP in DM patients

In non-diabetic patients, 24 out of 40 patients had SBP once and 16 patients were diagnosed twice during the study period. None of the patients was diagnosed three times and it contributed 60 % with once and 40 % with twice in the study period.

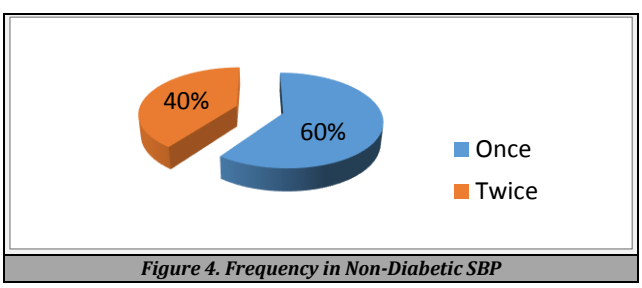

Figure 4. Frequency in Non-Diabetic SBP

The average frequency of SBP and variants was found to be 1.7 (diabetic-1.81, Non-diabetic-1.4) during the study period of 2 years.

	SBP- Less than 2 times	2 or More	Total
Diabetics	20 (27.08)[1.85]	44 (36.92)[1.36]	64
Non Diabetics	24 (16.92)[2.96]	16 (23.08)[2.17]	40
Total	**44**	**60**	**104**

Table 1. Comparison of Frequency of SBP in DM and Non-DM

Chi-square statistic is 8.3358 and p-value is 0.00388

DISCUSSION

There are many mechanisms in which cirrhosis contributes to impaired glucose metabolism but contributes to dysglycemia by interfering with the insulin-glucose metabolism, while DM predisposes to liver disease progression and a higher risk of serious complications of cirrhosis, presuming that patients with the compensated chronic liver disease and concomitant DM may be at greater risk of decompensating events. Usually, diabetes is classified as Type 1 (T1) and Type 2 (T2), besides T1 and T2DM, hepatogenous diabetes (HD) is a recently described and yet unrecognized clinical entity with particular physiopathological mechanisms and systemic complications. It can be defined as a state of impaired glucose regulation caused by altered liver function following cirrhosis. It typically presents with hyperinsulinemia, normal fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c), but the abnormal response to oral glucose tolerance test (OGTT). Like T2DM, HD might also be associated with an increased rate of complication. However, the clinical impact of HD on cirrhosis is yet to be elucidated, given the prognosis of patients who develop it. There are many risk factors for the development of SBP as mentioned in the literature, recent one among them is proton pump inhibitor usage[4-7,18] Presence of DM leads to significant changes in the gut microbiota.[14] Metagenome-wide association study analysis showed that patients with type 2 diabetes were characterized by a moderate degree of gut microbial dysbiosis, a decrease in the abundance of some universal butyrate-producing bacteria and an increase in various opportunistic pathogens, as well as an enrichment of other microbial functions conferring sulphate reduction and oxidative stress resistance.[14-15] Therefore, it would have been quite convincing if there had been a relevant change in the pathogens that are involved in SBP episodes in DM patients. Patients with DM and SBP may be risk factors for accelerated decompensation in cirrhotic patients.[12,13,14] Previous studies show that DM prevalence in cirrhotic patients is about 30-40 % and up to 50 % who are having bacterial infections are found to be having impaired glucose. In our study, more than 60 % of SBP patients were diabetics. Many experts considered DM as an independent factor for the development of SBP which was consistent with most of the study reports and inconsistent with few research papers.[18-21] SBP manifested in significantly higher diabetic patients and frequency found to be 2-3 times over 2 to 3 years as per literature available and frequency of SBP in a diabetic patient in the present study was 1.81, which was comparable with the available previous data.[16,20] Infections are the major risk factors for hospitalisation and mortality in cirrhotics.[22] It is also one of the most common comorbidities in type 2 diabetes mellitus (DM) affecting 20–40 % of cirrhotic patients.[5-7] In this study, the average risk for non-diabetics was found to be 1.4, which was lower compared to diabetics. Diabetic patients were found to have an increased frequency of SBP in comparison to the non-diabetic patient as per the present study. Comparison of frequency of SBP in diabetics and non-diabetics, chi-square test showed p-value 0.003, which was significant. These findings are consistent with previous studies.[18-21] In view of contradictory results in a few studies,[15-16,18,21] studies with large populations and parameters including prior antibiotic usage, antibiotic resistance, blood glucose control during episodes etc are needed.

CONCLUSIONS

The study showed that SBP frequency is significantly increased in diabetic patients in comparison with non-diabetics in cirrhosis. So there is a major role for diabetic control and frequent blood sugar monitoring in the management of cirrhosis. Thereby, for patients with cirrhosis, how to control blood glucose clinically and to what extent to minimize its impact on cirrhotic ascites with SBP should be one of the research agendas.

Limitations

In this study, HD was not separately considered, and type of diabetes was not taken into account. Limitations of the study considered are single centric, small study population, blood glucose status and other infective foci during the episode were not mentioned.

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