DOI: 10.7860/JCDR/2017/30705.10529

Original Article

Internal Medicine Section

Cirrhosis of Liver and Diabetes Mellitus: The Diabolic Duo?

THAZHATH MAVALI RAMACHANDRAN[1], ANINCHENT HARAYIL RAJAN RAJNEESH[2], GEORGE SARIN ZACHARIA[3], RAJENDRAN P ADARSH[4]

ABSTRACT

Introduction: Cirrhosis of the liver and diabetes mellitus are two chronic illnesses with significant impact on the quality of life. Studies from different part of the world have shown the combination to be associated with higher incidence of complications of cirrhosis and reduced survival. However, data on the impact of pre-cirrhotic and post-cirrhotic diabetes on cirrhosis is minimal.

Aim: The aim of the study was to determine the complications of cirrhosis patients with and without co-existent DM and to compare the relation between cirrhosis patients with antecedent DM and hepatogenous DM.

Materials and Methods: This was a prospective study conducted at a tertiary care hospital in Kerala, India, over a period of three years. Cirrhosis patients with and without diabetes, along with subcategorization as antecedent/hepatogenous diabetes, were studied for various complications and outcome including death. Chi-square and Mann-whitney tests were used for comparing data.

Results: Patients with cirrhosis and diabetes had higher incidence of gall stones (27.6% versus 13.2%; p=0.008) and urinary infection (29.3% versus 7.5%; p=<0.001). Incidence of hepatocellular carcinoma and mortality were similar between the groups. Patients with antecedent diabetes and hepatogenous diabetes were similar with respect to complications and mortality. Child-Turcotte-Pugh (CTP) score, Model for End stage Liver Disease (MELD) score, urinary tract and respiratory infections and duration of cirrhosis were independent predictors of mortality in patients with cirrhosis.

Conclusion: Coexistent diabetes mellitus increases the incidence of complications and hospitalizations in cirrhosis patients but without impact on mortality rates. There is no significant morbidity or mortality difference between cirrhotics with antecedent diabetes and hepatogenous diabetes.

Keywords: Carcinoma, Complications, Hepatocellular, Urinary tract infection

INTRODUCTION

Cirrhosis of liver and Diabetes Mellitus (DM) are two chronic illnesses with significant impact on the quality of life. The estimated prevalence of DM in cirrhosis is 12.3%-57% [1,2]. Impaired glucose tolerance is seen in around 80% of patients with cirrhosis whereas 30%-60% of patients with advanced cirrhosis develop diabetes [3,4]. Diabetes developing as a complication of cirrhosis is referred to as Hepatogenous Diabetes (HD) [3]. HD differs from type 2 DM in that it often lacks family history, has less frequent association with obesity, lesser incidence of micro and macrovascular complications and has greater incidence of hypoglycaemic episodes [3,4]. The knowledge on the pathophysiology of HD largely revolves around the concept of insulin resistance in liver cirrhosis. Insulin resistance is known to occur in the liver as well as peripherally in the muscles and in adipose tissue. Peripheral hyperinsulinemia in cirrhosis is postulated to result from decreased hepatic clearance of insulin and portosystemic shunting [5-7]. Kim MG et al., have demonstrated the Homeostatic Model Assessment (HOMA)-insulin resistance index to be significantly higher in patients with HD compared to type 2 DM [8]. Hyperinsulinemia in cirrhosis hence probably results from the combination of insulin resistance and increased pancreatic secretion. The complex insulin - counter-regulatory hormone interaction together with the various genetic and environmental factors including the aetiological factors like alcohol, viral Hepatitis C (HCV) and hereditary haemochromatosis are thought to result in HD [4-7,9].

The aetiology of chronic liver disease plays a crucial role in its relation to DM. Non-alcoholic fatty liver disease, alcoholic liver disease, haemochromatosis and HCV are found to be more frequently associated with DM [9-12]. DM is found to be associated with asymptomatic transaminase elevation, fatty liver, cirrhosis, and increased incidence of complications of cirrhosis liver including hepatocellular carcinoma [13,14]. The Verona diabetes study identifies cirrhosis as the fourth leading cause of death among diabetics (4.4% of diabetes related deaths) while according to the Paris prospective study cirrhosis causes 12.5% of deaths in diabetics [15,16].

Coexistence of DM and cirrhosis however is not indolent but often more ominous than each of these entities independently. Studies from various parts of the world have shown the combination to be associated with higher incidence of complications of cirrhosis and reduced survival irrespective of the aetiology of cirrhosis [9,14]. However, the data is sparse from the Indian subcontinent regarding the impact of DM on various facets of cirrhosis liver. Also, to the best of our knowledge no study from India till date has compared the differences between pre-cirrhotic and post-cirrhotic diabetes with respect to its impact on liver disease.

The primary aim of the current study was to compare the complications and mortality of cirrhosis patients with and without co-existent DM. Also, to determine differences in complications of cirrhosis patients with antecedent DM and hepatogenous DM.

MATERIALS AND METHODS

This prospective observational study was conducted at Government Medical College, Kozhikode, Kerala, India. Patients with diagnosis of cirrhosis liver and satisfying the inclusion criteria attending the Department of Gastroenterology from January 2009 to January 2011 were enrolled in the study and were regularly followed since enrolment until death or January 2013 whichever was earlier. Patients aged between 18 to 75 years with diagnosis of cirrhosis with or without antecedent DM were included in the study group.

The diagnosis of cirrhosis was based on a combination of history, physical examination, laboratory and radiological investigations and upper GI endoscopy. Diagnosis of DM, impaired fasting glucose and impaired glucose tolerance were based on the expert

committee follow up report on the diagnosis of diabetes mellitus; 2003 [17]. Patients with secondary diabetes, chronic pancreatitis, Hepatocellular Carcinoma (HCC) or other neoplasms at the time of enrolment, chronic renal failure, chronic cardio-respiratory illnesses and pregnant females were excluded from the study. Institutional Research and Ethical Committee approval were obtained to conduct the study. Informed written consent was obtained from patients before enrolment into the study.

All patients underwent complete haemogram, renal and liver biochemistries, serum electrolytes, α fetoprotein and abdominal sonogram at baseline. Child-Turcotte-Pugh (CTP) and Model for End stage Liver Disease (MELD) scoring were calculated using presence of ascites or encephalopathy, albumin, creatinine, bilirubin and International Normalised Ratio (INR) [18]. At each visit the patients were enquired about any major health related events or hospitalizations. Investigations were repeated six monthly in all patients or when hospitalised. Patients who failed to follow up regularly were contacted over telephone. Diagnostic paracentesis was performed at baseline in patients with ascites or at development of ascites while on follow up and or whenever there was clinical suspicion of Spontaneous Bacterial Peritonitis (SBP). Development of SBP, other infections/sepsis, hepatic encephalopathy, renal failure, hepatocellular carcinoma as well as death were noted. Patients were assigned into two groups; patients with cirrhosis and diabetes (Group A), and patients with cirrhosis without DM (Group B). Patients with cirrhosis and diabetes were further sub grouped as those with diagnosis of diabetes prior to the diagnosis of cirrhosis {Antecedent Diabetes (AD)} and those having diagnosis of diabetes after detection of cirrhosis (hepatogenous diabetes or HD). Demography, aetiology, laboratory data and the disease course over the follow up period were compared between Group A and B as well as between AD and HD.

STATISTICAL ANALYSIS

Quantitative variables were expressed as mean ± standard deviation and compared using t-test or Mann Whitney U test. Categorical variables were compared using Chi-square test. Predictors of mortality were analysed initially using univariate analysis and those found statistically significant were put into a multivariate forward conditional logistic regression to obtain the best model with adjusted odds ratios and 95% confidence intervals. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 291 patients were found to be eligible for the study. Out of this, 69 patients lost to follow up and hence excluded from analysis and the rest 222 patients were included in the final analysis. A total of 116 patients had DM and cirrhosis, of which 59 were diagnosed to have HD while 48 had AD and nine patients had a simultaneous diagnosis of cirrhosis and diabetes. Alcohol and cryptogenic cirrhosis were the most common cause in both the groups, followed by hepatitis B and C. During the course of study, majority of patients were euglycaemic (n=106/222).

Patients were divided into cirrhosis with diabetes (Group A) and cirrhosis without diabetes (Group B) and baseline characteristics are depicted in [Table/Fig-1].

Mean age of patients were 54.90 years in Group A and 54.05 years in Group B. In the study, 96 (82.76%) of those with diabetes and 88 (83.02%) of those without diabetes were males. The mean duration of diabetes was 35.04 months for the entire diabetic cohort. Also, 55 (47.4%) of those with diabetes and 63 (59.4%) of non-diabetics gave history of alcohol consumption in cirrhogenic doses. Duration of cirrhosis in months was 20.05 and 19.63 respectively for Group A and B. The CTP and MELD scores were 9.96 and 16.21 in Group A versus 9.90 and 16.02 in Group B. The total serum bilirubin, albumin and Prothrombin Time (PT) prolongation were 3.80 mg/dl, 2.81 gm/dl and 6.1 seconds for Group A while were 3.76 mg/dl, 2.97 gm/dl and 6.01 seconds in Group B respectively. Mean serum ferritin level was 215.1 ng/ml in Group A while it was 111.92 ng/ml in Group B. Diabetic patients were hospitalised for a mean of 3.82 times (24.03 days) while non-diabetics were admitted 3.24 times (16.91 days). The mean number of upper gastrointestinal bleed and spontaneous bacterial peritonitis were 1.76 and 0.63 versus 1.30 and 0.59 for Group A and B respectively. Baseline demographic, clinical and laboratory variables of patients are summarized in [Table/Fig-1].

Parameters	Group A [n=116, (Mean ± SD)]	Group B [n=106 (Mean ± SD)]	p-value
Age (years)	54.90±9.04	54.05±10.95	0.528
Duration of cirrhosis (months)	20.05±20.34	19.63±17.66	0.870
Total bilirubin (mg/dl)	3.80±4.12	3.76±3.26	0.926
Albumin (gm/dl)	2.81±0.55	2.97±0.47	0.017*
PT# prolongation (seconds)	6.10±3.85	6.01±3.87	0.864
CTP/Child turcotte pugh score	9.96±2.69	9.90±2.67	0.866
MELD# score	16.21±5.51	16.02±6.13	0.810
Hemoglobin (gm/dl)	9.95±1.91	9.76±1.83	0.483
Total leukocyte count (cells/mm^3)	7302.32±3995.51	7132.08±2466.60	0.706
Platelet count (lakh cells/mm^3)	0.98±0.64	1.09±0.51	0.168
Creatinine (mg/dl)	1.20±0.69	1.12±0.58	0.330
Sodium (mEq/L)	130.55±6.58	129.56±6.42	0.256
Ferritin (ng/ml)	215.10±179.59	111.92±79.89	<0.001*

[Table/Fig-1]: Comparison of baseline variables between patients with cirrhosis and diabetes [Group A] and cirrhosis with no diabetes [Group B].
#PT=Prothrombin time, MELD=Model for end stage liver disease; *:statistically significant (t test used to compare data)

Cirrhosis with Antecedent Diabetes Versus Hepatogenous Diabetes

Mean age of patients were 55.58 years and 54.51 years in HD and AD groups respectively. In the study, 41 (85.4%) of those with AD and 46 (78%) of those with HD were males. The mean duration of diabetes in months was 70.71 and 7.80 for HD and AD respectively. Duration of cirrhosis in months was 13.31 and 25.02 respectively for HD and AD groups. The CTP and MELD scores were 9.96 and 15.50 in HD patients while it was 9.90 and 15.85 in AD patients. The total serum bilirubin, albumin and PT prolongation were 3.90 mg/dl, 2.85 g/dl and 5.58 seconds for HD patients while were 3.45 mg/dl, 2.75 g/dl and 6.27 seconds in AD patients. The mean serum ferritin levels were 228.94 ng/ml in HD arm while it was 203.35 ng/ml in AD arm. Baseline demographic, clinical and laboratory variables of patients are summarized in [Table/Fig-2]. Complications and mortality were compared among the study patients and are depicted in [Table/Fig-3]. Urinary Tract Infection (UTI) was more common amongst diabetics [29.3% versus 7.5%; p=<0.001] while cellulitis and Lower Respiratory Tract Infections (LRTI) were similar across the groups. Gallstones were significantly more common amongst diabetic cirrhotics (27.6% vs 13.2%, p=0.008).

Predictors of Mortality

A total of 95 (42.8%) patients expired during the study period; 53 (45.7%) in the diabetic arm and 42 (39.6%0 in the non-diabetic arm. The mortality rates were not statistically significant between the two arms (p=0.361). The mean duration of cirrhosis in months was significantly more in patients who died (24.79 versus 16.16; p=0.001). Majority of patients with cirrhosis who died belonged to

Parameters	Group HD[n=59,(Mean ± SD)]	Group AD[n=48,(Mean ± SD)]	p-value
Age (years)	55.58±8.64	54.51±9.90	0.556
Duration of cirrhosis (months)	13.31±14.85	25.02±21.95	0.002*
Duration of DM (months)	70.71±51.59	7.80±10.96	<0.001*
Total bilirubin (mg/dl)	3.90±5.15	3.45±3.11	0.579
Albumin (gm/dl)	2.85±0.60	2.75±0.54	0.389
PT* prolongation (seconds)	5.58±4.07	6.27±3.48	0.346
CTP/Child turcotte pugh score	9.96±2.69	9.90±2.67	0.808
MELD* score	15.50±5.60	15.85±4.80	0.730
Hemoglobin(gm/dl)	10.36±1.98	9.64±1.84	0.054
Total leukocyte count (cells/mm^3)	7527.29±3710.49	7197.61±4445.47	0.682
Platelet count (lakh cells/mm^3)	1.05±0.69	0.94±0.63	0.417
Creatinine (mg/dl)	1.23±0.88	1.09±0.42	0.258
Sodium (mEq/L)	130.48±5.09	130.80±7.33	0.800
Ferritin (ng/ml)	228.94±164.61	203.35±197.91	0.475

[Table/Fig-2]: Comparison of baseline variables between Hepatogenous diabetes [HD] and Antecedent diabetes [AD].
*PT=Prothrombin time, MELD=Model for end stage liver disease; *:statistically significant (t test used to compare data)

Parameters	A	B	p-value	AD	HD	p-value
Cellulitis	16.7%	11.3%	0.394	16.7%	18.6%	0.913
UTI#	29.3%	7.5%	<0.001*	31.2%	28.8%	0.535
LRTI#	25.9%	22.6%	0.576	31.3%	22%	0.281
Gall stones	27.6%	13.2%	0.008*	31.3%	27.1%	0.639
HCC#	11.8%	7.5%	0.290	16.7%	6.8%	0.107
Deaths	45.7%	39.6%	0.361	43.8%	45.8%	0.835

[Table/Fig-3]: Comparison of complications in the study groups.
#UTI: Urinary tract infection, LRTI: lower respiratory tract infection, HCC: Hepatocellular carcinoma; *:statistically significant (t test used to compare data)

child class C (n=77, 81.1%). UTI, LRTI and SBP were significantly more common in those cirrhosis patients who had a fatal outcome (p=0.002, 0.005, <0.001 respectively). [Table/Fig-4] compares patients who died versus those who survived in the current study. Logistic regression identified a model (Cox and Snell R^2 value is a goodness of fit statistics used in logistic regression to evaluate the goodness of model; A value of 0.387 indicate 38.7% variability in outcome can be explained by the model parameters together) with following variables-Child (CTP) score, MELD score, UTI, LRTI and duration of cirrhosis as predictors of mortality as shown in [Table/Fig-5].

DISCUSSION

Cirrhosis is known to cause dysglycaemia by a variety of mechanisms while diabetes predisposes patients to serious liver diseases [19]. DM has also been demonstrated to have significant impact in patients with cirrhosis making the association more ominous than expected. DM is found to be associated with greater incidence of complications and mortality in cirrhosis [19].

In cirrhotic patients with and without diabetes, most of the baseline characteristics were comparable. Diabetic patients had lower albumin compared to non diabetics, which maybe secondary to albuminuria in diabetes, which is more pronounced in cirrhosis [20,21].

The serum ferritin levels were significantly higher in cirrhosis with diabetes. High ferritin in diabetes is well described in studies

Variables	Survived	Died	p-value
Quantitative variables (Expressed as mean+/-SD)			
Age (years)	54.76±10.0	54.13±9.9	0.639
Duration of cirrhosis (months)	16.16±15.9	24.79±21.6	0.001*
Duration of DM (months)	15.76±39.2	21.72±43.4	0.287
Total bilirubin (mg/dl)	2.32±1.6	5.74±4.6	<0.001*
Albumin (gm/dl)	3.08±0.44	2.62±0.49	<0.001*
PT# prolongation (seconds)	4.65±2.6	7.94±4.3	<0.001*
CTP/Child turcotte pugh score	8.6±2.1	11.7±2.2	<0.001*
MELD# score	13.45±3.8	19.68±6.0	<0.001*
Hemoglobin (gm/dl)	10.12±1.80	9.51±1.89	0.015*
Total leukocyte count (cells/mm^3)	6703.69±2228	7912.63±4340	0.007*
Platelet count (lakh cells/mm^3)	1.14±0.6	0.90±0.4	0.002*
Creatinine (mg/dl)	1.03±0.3	1.35±0.8	<0.001*
Sodium (mEq/L)	131.61±5.7	128.03±6.8	<0.001*
Ferritin (ng/ml)	162.65±150	170.63±150	0.681
Number of hospitalisations	3.28±1.9	3.88±2.3	0.040*
Duration of hospitalisation (days)	17.27±11.5	25.12±15.0	<0.001*
Number of SBP# episodes	0.39±0.6	0.92±0.9	<0.001*
Number of variceal bleed episodes	1.51±1.3	1.58±1.6	0.951
Categorical variables			
Male sex (%)	85.83	78.95	0.178
DM# (%)	49.61	55.79	0.361
Aetiology (Alcohol: Cryptogenic: Others) (%)	54.3: 34.6: 11	51.6: 38.9: 9.5	0.899
CTP Class A: B: C (%)	15.7: 49.6: 34.7	2.1: 16.8: 81.1	<.001*
UTI# (%)	11.02	29.47	0.002*
LRTI# (%)	17.32	33.68	0.005*
Cellulitis (%)	10.24	18.95	0.064
HCC# (%)	7.09	12.63	0.162

[Table/Fig-4]: Comparison of variables and complications between patients who survived and died.
#PT:Prothrombin, MELD: Model for end stage liver disease, SBP: spontaneous bacterial peritonitis, DM: diabetes mellitus, UTI: Urinary tract infection, LRTI: Lower repiratory tract infection, HCC: Hepatocellular carcinoma; *:statistically significant (t test used to compare data)

Variables	Odds ratio	95% confidence interval	p-value
CTP/Child turcotte pugh score	1.42	1.17 - 1.72	<0.001
MELD* score	1.16	1.06 - 1.27	0.002
UTI*	2.50	1.04 - 5.99	0.041
LRTI*	2.26	0.99 - 5.17	0.053
PT# prolongation (seconds)	1.02	1.00 - 1.04	<0.001

[Table/Fig-5]: Analysis showing various predictors of mortality among patients with cirrhosis and diabetes.
*MELD: Model for end stage liver disease, UTI: Urinary tract infection, LRTI: Lower respiratory tract infection. Cox and Snell regression analysis test used.

[22,23]. Lecube A et al., had shown that patients with chronic hepatitis C infection had higher ferritin levels and was secondary to concomitant diabetes rather than the infection proper [24]. The exact mechanism of high ferritin levels in diabetes is still unclear. It has been demonstrated that the ferritin levels will be elevated in chronic inflammatory disease, which is one of postulated cause of diabetes [25-27].

Our study has found the occurrence of complications were more in the diabetes group than the non-diabetes group. The incidence of urinary tract infections and gall stones were significantly more in diabetic cirrhotics than non-diabetics. Previous studies in cirrhosis patients have demonstrated the higher incidence of bacterial

infections in those with DM, owing to its immunosuppressive effects [28-32]. In the current study, the incidence of LRTI and SBP was however not different between the diabetic and non-diabetic patients, cirrhosis per se is associated with a greater incidence of gall stones but mostly asymptomatic [33,34]. The postulated mechanisms for the increased risk of gall stones in cirrhosis include haemolysis secondary to hypersplenism, hyperestrogenism, alterations in the composition of bile due to aberrations in hepatic synthesis and transport of bile salts as well as unconjugated bilirubin [35]. Likewise, DM by itself is a risk factor for gall stone disease even in the general population [36]. Considering the increased risk of gall stones in DM and cirrhosis it is logically expected that the incidence of gall stones is more in cirrhosis with DM than those without diabetes. In the current study, only 10.9% patients had symptoms pertaining to gall stone disease, while the rest where silent gall stones detected during abdominal sonogram.

Another finding from this study is the increased incidence of portal hypertensive upper gastrointestinal bleeds in patients with cirrhosis and diabetes. A recent study had concluded that insulin resistance and hepatogenous diabetes were having a positive correlation with portal hypertension and variceal bleeding [37].

In our study, there was no statistically significant difference in the incidence of HCC or death even though both were slightly higher in the diabetic group. There is mounting body of evidence in medical literature to suggest an increased risk of HCC in type 2 DM. Patients with cirrhosis related to alcohol, hepatitis viruses B or C when associated with DM are found to have higher risk of HCC [38,39]. Some studies have demonstrated an increased mortality in cirrhosis patients with diabetes [40-43]. The increased mortality was however not due to the classical diabetes-related complications, but mostly due to liver disease related complications. The prognostic significance of DM was relevant only when patients who died of gastrointestinal bleeding, were excluded [43]. Also, most of the studies that had identified DM as a prognostic variable were long term studies with a mean follow up period more than five years suggesting that DM might be a long term prognostic variable [43-46]. The shorter follow up duration in the current study might have contributed to the non-significance of the potential adverse prognostic impact of DM on cirrhosis.

In cirrhotic patients with antecedent and hepatogenous diabetes, incidence of complications was almost similar except for upper GI bleeds, hospitalizations, HCC and deaths. HD is postulated to increase the morbidity and mortality associated with cirrhosis [3]. The postulated mechanisms are however similar to those operating in patients with cirrhosis and AD [3,43]. The current study did not reveal any difference in complications or prognosis of liver disease between the two groups.

Greater duration of cirrhosis, higher CTP and MELD scores were associated with mortality. More PT prolongation, increased total bilirubin, creatinine, low levels of platelets, sodium and albumin were associated with poorer outcome. UTI and LRTI as well as SBP were also associated with higher mortality. Number of hospital admissions was also more common in patients who expired. Diabetes, antecedent or hepatogenous was not found to be a predictor of mortality in cirrhosis. Logistic regression revealed CTP score, MELD score, UTI, and duration of cirrhosis to be independent predictors of mortality. The findings in the current study are consistent with published literature with respect to most of the analysed variables [43-47].

LIMITATION

The major limitation of the study was shorter follow up. Cirrhosis and DM both being long term diseases the current short duration of study might have missed atleast some of the impacts of DM on cirrhosis liver. Again it is always possible that either of cirrhosis or diabetes might have developed initially and had remained undiagnosed until evaluated for the other, thereby confounding the diagnosis of HD versus AD. Yet another limitation is that an oral glucose tolerance test has not been performed for any of the patients included in the study. If it was performed it might have led to identification of a few patients with impaired glucose tolerance but without overt DM. Inadvertently this might have led to misclassifying atleast some patients as having no diabetes.

CONCLUSION

In conclusion, co-existent diabetes increases the incidence of complications in patients with cirrhosis. Although, AD and HD did not show significant differences in outcome, it is worth mentioning separately to characterize natural history of diabetes in cirrhotics. Antecedent and hepatogenous diabetes are less described entities in most of the studies and requires longer follow up studies to understand the progression of disease.

AUTHORS' CONTRIBUTION

All the authors have contributed enough towards this publication to justify authorship criteria. TMR designed the study, recruited patients, collected the clinical and laboratory data and participated in manuscript preparation. AHRR participated in patient recruitment and data collection. GSZ prepared the manuscript. RPA edited the manuscript. The manuscript has been read and approved by all the authors. We warrant that this manuscript is original and has not been in part or in whole simultaneously submitted to or published in another journal.

ACKNOWLEDGEMENTS

We acknowledge Dr. Biju George (Assistant Professor, Social and Preventive Medicine, Govt. Medical College, Kozhikode) for his wholehearted help with statistical analysis.

REFERENCES

[1] Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. Alimentary Pharmacology & Therapeutics. 2005;22(s2):24-27.
[2] Pazhanivel M, Jayanthi V. Diabetes mellitus and cirrhosis liver. Minerva Gastroenterologica E Dietologica. 2010;56(1):7-11.
[3] García-Compean D, Jaquez-Quintana JO, Maldonado-Garza H. Hepatogenous diabetes- Current views of an ancient problem. Ann Hepatol. 2009;8(1):13-20.
[4] García-Compeán D, Jáquez-Quintana JO, Lavalle-González FJ, Reyes-Cabello E, González-González JA, Muñoz-Espinosa LE, et al. The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis. A prospective study. Ann Hepatol. 2012;11:240-48.
[5] Tappy L, Minehira K. New data and new concepts on the role of the liver in glucose homeostasis. Current Opinion in Clinical Nutrition & Metabolic Care. 2001;4(4):273-77
[6] Petrides AS, Stanley T, Matthews DE, Vogt C, Bush AJ, Lambeth H. Insulin resistance in cirrhosis: prolonged reduction of hyperinsulinemia normalizes insulin sensitivity. Hepatology. 1998;28(1):141-49.
[7] Merli M, Leonetti F, Riggio O, Valeriano V, Ribaudo MC, Sprati F, et al. Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. Hepatology. 1999;30(3):649-54.
[8] Kim MG, Choi WC. Differential Diagnosis of Diabetes Mellitus caused by Liver Cirrhosis and Other Type 2 diabetes mellitus. Korean J Hepatol. 2006;12(4):524-29.
[9] Greco AV, Mingrone G, Mari A, Capristo E, Manco ME, Gasbarrini G. Mechanisms of hyperinsulinaemia in Child's disease grade B liver cirrhosis investigated in free living conditions. Gut. 2002;51(6):870-75.
[10] Harrison SA. Liver disease in patients with diabetes mellitus. Journal of Clinical Gastroenterology. 2006;40(1):68-76.
[11] Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Annals of Internal Medicine. 2000;133(8):592-99.
[12] Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. Journal of Hepatology. 2000;32(2):209-17.
[13] Niederau CL, Fischer RU, Purschel A, Stremmel WO, Haussinger D, Strohmeyer GE. Long-term survival in patients with hereditary haemochromatosis. Gastroenterology. 1996;110(4):1107-19.
[14] Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care. 2007;30(3):734-43.
[15] De Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. Diabetes care.

1999;22(5):756-61.
[16] Balkau B, Eschwege E, Ducimetère P, Richard JL, Warnet JM. The high risk of death by alcohol related diseases in subjects diagnosed as diabetic and impaired glucose tolerant: the Paris Prospective Study after 15 years of follow-up. Journal of Clinical Epidemiology. 1991;44(6):465-74.
[17] Kahn R. Follow-up report on the diagnosis of diabetes mellitus: the expert committee on the diagnosis and classifications of diabetes mellitus. Diabetes care. 2003;26(11):3160.
[18] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
[19] Porepa L, Ray JG, Sanchez-Romeu P, Booth GL. Newly diagnosed diabetes mellitus as a risk factor for serious liver disease. Canadian Medical Association Journal. 2010;182(11):E526-31.
[20] Quintana JO, García-Compean D, González JA, Pérez JZ, González FJ, Espinosa LE, et al. The impact of diabetes mellitus in mortality of patients with compensated liver cirrhosis-a prospective study. Ann Hepatol. 2011;10(1):56-62.
[21] Parving HH, Rossing N, Nielsen SL, Lassen NA. Increased transcapillary escape rate of albumin, IgG, and IgM after plasma volume expansion. American Journal of Physiology--Legacy Content. 1974;227(2):245-50.
[22] Raj S, Rajan GV. Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus.
[23] Kaye TB, Guay AT, Simonson DC. Non-insulin-dependent diabetes mellitus and elevated serum ferritin level. Journal of Diabetes and its Complications. 1993;7(4):245-49.
[24] Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, García L, et al. Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection. Diabetes Care. 2004;27(11):2669-75.
[25] Konijn AM, Hershko C. Ferritin synthesis in inflammation: I. Pathogenesis of impaired iron release. British Journal of Haematology. 1977;37(1):7-16.
[26] Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. Diabetes. 2002;51(8):2348-54.
[27] Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor α and blood cytokine production in type 2 diabetes. Life sciences. 2000;67(3):291-300.
[28] Garcia-Tsao G. Bacterial infections in cirrhosis: treatment and prophylaxis. Journal of hepatology. 2005;42(1):S85-92.
[29] Cheruvattath R, Balan V. Infections in patients with end-stage liver disease. Journal of Clinical Gastroenterology. 2007;41(4):403-11.
[30] Amato A, Precone DF, Carannante N, Brancaccio G, Stornaiuolo G, Galante D, et al. Prevalence and risk factors for bacteriuria in patients with cirrhosis. Infez Med. 2005;13(2):103-08.
[31] Díaz FJ, Román R, Ulloa V, Monge E. Diabetes as a risk factor for infections in cirrhotic patients. Revista de gastroenterologia del Peru: organooficial de la Sociedad de Gastroenterologia del Peru. 2009;30(1):11-16.
[32] Wlazlo N, van Greevenbroek MM, Curvers J, Schoon EJ, Friederich P, Twisk JW, et al. Diabetes mellitus at the time of diagnosis ofcirrhosis is associated with higher incidence of spontaneous bacterial peritonitis, but not with increased mortality. Clinical Science. 2013;125(7):341-48.
[33] Sarin SK, Guptan RC, Malhotra S. Increased frequency of gallstones in cirrhotic and non-cirrhotic portal hypertension. The Journal of the Association of Physicians of India. 2002;50:518-22.
[34] Acalovschi M, Badea R, Dumitrascu D, Varga C. Prevalence of Gallstones In Liver Cirrhosis: A Sonographic Survey. American Journal of Gastroenterology. 1988;83(9):954-56.
[35] Conte D, Fraquelli M, Giunta M, Conti CB. Gallstones and liver disease: an overview. J Gastrointestin Liver Dis. 2011;20(1):9-11.
[36] Pagliarulo M, Fornari F, Fraquelli M, Zoli M, Giangregorio F, Grigolon A, et al. Gallstone disease and related risk factors in a large cohort of diabetic patients. Digestive and Liver Disease. 2004;36(2):130-34.
[37] Jeon HK, Kim MY, Baik SK, Park HJ, Choi H, Park SY, et al. Hepatogenous diabetes in cirrhosis is related to portal pressure and variceal haemorrhage. Digestive Diseases and Sciences. 2013;58(11):3335-41.
[38] El-serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126(2):460-68.
[39] Veldt BJ, Chen W, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology. 2008;47(6):1856-62.
[40] Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. Journal of Gastroenterology and Hepatology. 2002;17(6):677-81.
[41] Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. Hepatology. 1994;20(1):119-25.
[42] Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. The American Journal of Gastroenterology. 2006;101(1):70-75.
[43] Moscatiello S, Manini R, Marchesini G. Diabetes and liver disease: an ominous association. Nutrition, Metabolism and Cardiovascular Diseases. 2007;17(1):63-70.
[44] Orrego H, Israel Y, Blake JE, Medline A. Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. Hepatology. 1983;3(6):896-905.
[45] Angeli P, Wong F, Watson H, Ginès P. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology. 2006;44(6):1535-42.
[46] Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. Journal of Hepatology. 2004;40(6):897-903.
[47] Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child–Pugh versus MELD. Journal of Hepatology. 2005;42(1):S100-07.

PARTICULARS OF CONTRIBUTORS:
1. Additional Professor, Department of Medical Gastroenterology, Government Medical College, Kozhikode, Kerala, India.
2. Senior Resident, Department of Medical Gastroenterology, Government Medical College, Kozhikode, Kerala, India.
3. Senior Resident, Department of Medical Gastroenterology, Government Medical College, Kozhikode, Kerala, India.
4. Senior Resident, Department of Medical Gastroenterology, Government Medical College, Kozhikode, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Thazhath Mavali Ramachandran,
Additional Professor, Department of Medical Gastroenterology, Government Medical College, Kozhikode-673008, Kerala, India.
E-mail: drtmram@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 05, 2017**
Date of Peer Review: **Jun 21, 2017**
Date of Acceptance: **Aug 08, 2017**
Date of Publishing: **Sep 01, 2017**