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Original Article

Comparing Frequency of Cardiovascular Autonomic Neuropathy in Diabetic Cirrhotic with Non-Diabetic Cirrhotic Patients

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ABSTRACT

Cardiac autonomic neuropathy is most common secondary complication of diabetes mellitus (DM) is frequently undiagnosed and neglected complication even though it is an independent predictor of mortality and morbidity. **Objective:** To determine and compare the frequency of cardiovascular autonomic neuropathy in diabetic cirrhotic and non-diabetic cirrhotic patients. **Methods:** Cross sectional study was done on 120 patients enrolled in Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan. Two groups, diabetic cirrhotic and non-diabetic cirrhotic patients were enrolled. Those diabetic cirrhotic patients were selected, who had controlled glycaemic levels due to proper medication, and patients of both groups had a definite diagnosis of cirrhosis liver. Cardiac autonomic neuropathy was determined in each patient using five standard tests. There after Bellavere,s scoring system was applied to assess the extent of cardiac autonomic dysfunction in each subject. **Results:** There were 33 males and 27 females in diabetic cirrhotic group and 31 males and 29 females in non-diabetic cirrhotic group. The mean age was 57.48 ± 10.80 years in diabetic cirrhotic patients whereas in the non-diabetic cirrhotic patients, mean age was 51.92 ± 14.21 years. In the diabetic cirrhotic group, 52 patients had parasympathetic tests derangement and 50 patients had sympathetic tests derangement. In non-diabetic cirrhotic group, 48 patients had parasympathetic tests derangement and 47 patients had sympathetic test derangement. After analysing the results of frequency of cardiovascular autonomic neuropathy, the comparison between the two groups revealed that there is no significant difference between the two groups. **Conclusions:** This study shows that cardiovascular autonomic neuropathy develops frequently in cirrhotic subjects, that it is found with comparable frequency in diabetics and non-diabetics, and it increases in severity with increase in severity of liver damage, suggesting that liver damage contributes to the neurological deficit.

INTRODUCTION

Diabetes Mellitus (DM) is a multifactorial disorder marked by hyperglycaemia that may be caused either due to defective insulin action, secretion, or both. Following are two types of diabetes mellitus "Type 1 and Type 2 Diabetes Mellitus"("T1DM & T2DM" respectively) and the other type which is most important is Gestational Diabetes Mellitus (GDM) [1,2]. Abbreviated as (DAN)" diabetic autonomic neuropathy is known as one of the most common complexities of diabetes, but it is the most neglected. In diabetic patients, damage to parasympathetic and/or sympathetic nerves occurs causing peripheral neuropathy excluding other causes of neuropathy. In type 1 diabetes, variation in the prevalence of

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DAN ranges from 1% to 90% and in type 2 it ranges from20% to 73% [3,4].

Autonomic Nervous System (ANS) is responsible for regulating involuntary functions of the body which include cardiac, intestinal, respiratory, and endocrine functions. ANS is organized as a reflex arc, which contains both afferent and efferent parts, finally integrate in the CNS [3]. Autonomic neuropathy is defined as "a peripheral neuropathy with selective or disproportionate involvement of autonomic fibres" [5]. Clinical manifestations of the disease are versatile on account that the autonomic innervation extends to all the organs [6-8].

The serious complication developing consequent to the DM is cardiac autonomic neuropathy (CAN) that leads to serious morbidities or mortalities [9]. Cirrhotic liver is another risk factor causing cardiovascular autonomic neuropathy. The CAN is proved to be life threatening as it indicates the cardiovascular mortality mostly due to cardiac arrhythmias [10]. CAN have three stages; a deep breath alone impairs heart rate, an abnormal response to the valsalva maneuver at the intermediate stage and a postural hypotension is detected at the severe stage [11]. A variety of clinical studies have been conducted on cardiac autonomic nerve function since non-invasive tests are available for more than two decades [12]. Study uses CAN can be tested at the bedside by carrying out a battery of cardiovascular reflex tests. These tests include evaluating heart rate variability (HRV) with deep breathing, the valsalva maneuver ratio, the response of blood pressure to deep breathing reflected in the 30/15 ratio, and blood pressure response to standing posture. In previous studies, Ewing's criteria were used for evaluating cardiac autonomic nerve function, but in the present study, Bellavere's scoring is used [13]. Since chronic liver disease has increased dramatically in Pakistan, there is a dire need to study the function of the ANS in the cardiovascular system. A non-invasive test of cardiovascular ANS will determine the frequency of CAN in patients with and without type 2 DM in our tertiary care hospital with cirrhotic liver.

No study has been attempted to date that will show effect of comorbidity of diabetes and cirrhosis on frequency of autonomic neuropathy. So its early detection and timely management is needed to prevent cirrhotic and diabetic cardiomyopathy. So, our objectives are to determine and compare the frequency of cardiovascular autonomic neuropathy in diabetic and non diabetic cirrhotic patients.

METHODS:

Study Setting

This descriptive cross-sectional study was carried out in the Outpatient and inpatient Department of Medical unit (Gastroenterology) in Mufti Mehmood Memorial Teaching hospital Dera Ismail Khan from February 2018 to December 2018. It is the largest hospital of the Khyber Pakhtunkwa province, covering more than 20 districts and patients from tribal areas also look for care at the hospital.

Study Population

A total number of sixty diabetic cirrhotics and sixty non-diabetic cirrhotics patients were enrolled in the study. Inclusion criteria of these patients are present in Box 1. The patients were categorized in following way; Group 1: Patients who were diabetic and had cirrhosis, Group 2: Patients who were non-diabetic and cirrhosis. History was recorded on a proforma regarding evidence of chronic liver diseases & autonomic dysfunction. The patients were advised to abstain from drinking coffee overnight. Blood sugar was monitored, and samples were not taken if there was overnight hypoglycemic episode. Patients of chronic liver disease (primary eligibility criteria), aged between 20-80 years, either gender and who were stable hemodynamically for at least 48 hours, after admission were included.

General Physical Examination

Physical examination was done especially resting tachycardia, anemia, jaundice, edema, cyanosis, palmer erythema, finger clubbing, dehydration, erectile dysfunction, orthostatic hypotension, palpable lymph nodes and systemic examination including respiratory, gastrointestinal, cardiovascular, and central nervous system.

Hematological and Biochemical Profiles

Hematological and biochemical profiles were made in the pathology laboratory of Mufti Mehmood hospital. Investigations of complete blood count, prothrombin time, activated prothrombin time, erythrocyte sedimentation rate, blood electrolytes, ALT, AST, ALP, serum ammonia, total protein, serum albumin,Direct bilirubin, Indirect bilirubin, Free T4, TSHand ultrasound abdomen were also prepared.

Cardiovascular Autonomic Function Tests

These tests were performed by using ECG machine (Nihon Kohden RM -6000 Polygraph system, Japan), modified Mercury manometer (Portapres, TNO, The Netherlands) and modified Sphygmomanometer (Automated Welch Allyn,Welch Allyn Inc, NY, USA)

As outlined below, all patients underwent five standard tests of autonomic function.

Valsalva maneuver

The subject was instructed to attain supine posture and was given a mouthpiece to blow into and maintain the pressure at

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40 mm of Hg for 15 seconds. During this time ECG was recorded. This maneuver was asked to be performed in triplicates. Subject was given time to rest between the readings. The subject was instructed to sit quietly and then asked toput mouthpiece within the lips which was attached to the manometer for pressure observation. After taking a deep breath subject was asked to blow into the mouth piece while recording the start and stop time with the help of a stop watch for time observation. Blow force was kept at a pressure of 40 mm Hg on mercury manometer for 15 seconds and during this period a continuous electrocardiogram (ECG) was recorded in lead II. This maneuver was asked to be performed in triplicates with one min gap and results were articulated as:

Valsalva maneuver ratio = After performing the maneuver, the longest R-R interval value +during the maneuver, the shortest R-R interval value.

Change in heart rate in response to valsalva maneuver was assessed in the following way.

Following equation was used to calculate Valsalva ratio.

Valsalva ratio = longest R – R interval after the maneuver + shortest R

R interval during the maneuver

The mean of the three tests was considered the final value.

R-R Interval Measurement

The subject was instructed to breathe deeply for one minute in a way that he should inhail for five seconds and exhale for five seconds for record of the variation in heart rate (R-R interval) during deep breathing, so the subject has had six breaths/min. Lead II ECG was also recorded during the period of deep breathing. Marking was done on the ECG paper. During each breathing cycle the maximum and minimum R-R intervals were marked on the ECG paper. ECG paper was calibrated according to the following values: One big box = 0.2 seconds, Two big boxes= 0.4 seconds, Three big boxes = 100 seconds, Four big boxes = 75 seconds, Five big boxes = 60 seconds. The boxes between the two R-R intervals were counted; its value was identified as written above and then the heart rate was measured with a formula: Heart rate in beats/minute = 60 / (R-R interval). The result of the test was calculated as: R-R interval = Maximum heart rate – minimum heart rate (in six measured cycles). Using the mean of the six cycle measurements and the minimum and maximum heart rates in beats/min, the final value was calculated.

Heart Rate Response to Standing

These responses were performed according to the protocol by Ewing et al [14], in which the subject was instructed to lye gently on a sofa, recording the heart rate constantly on an electrocardiograph. The patient is asked to standup without support, and a mark was made on the ECG paper as soon as they stood. R-R intervals were the longest at or around the 30th beat and shortest at or around the 15th beat after standing. These intervals were measured with the calibration of ECG paper, as done in heart rate response during deep breathing. Standing caused a typical 30:15 ratio for the immediate response in heart rate.

Blood Pressure Response to Standing

Response of blood pressure to standing was performed by measuring the subject's blood pressure with a sphygmomanometer during the position when he/she was lying quietly and recorded [14]. The patient was asked to stand up and blood pressure is measured after one minute. The difference between the systolic blood pressure standing and the systolic blood pressure lying was taken as the postural fall in blood pressure. To calculate the mean, the test result was expressed as the mean and test was repeated three times.

Blood Pressure Response to Sustained Hand Grip

The subject was instructed to grip the inflatable rubber bag for which a customized sphygmomanometer was used. In support of continued hand grip, the subject was asked to apply maximum voluntary pressure possible. During maximum voluntary contraction, a reading was taken from the attached mercury manometer. Patient was instructed to put maximum possible force on the inflatable rubber bag and retain the hand grip for five minutes and this voluntary hand contraction was maintained up to 30%. Blood pressure was measured at one minute intervals during these five minutes of handgrip. Before the handgrip began was calculated and recorded, the mean of the three diastolic blood pressure readings was taken. The result was expressed as the difference between the two recorded values. The autonomic functions tests were graded according to the Bellavere's criteria, which is described in the table 2.1 [15]. Cardiac autonomic Function tests used for parasympathetic dysfunction are: Response of heart rate to valsalva maneuver, Variation of heart rate to deep breathing and Immediate response of heart rate to standing. Cardiac autonomic function tests used for sympathetic dysfunction are: Response of blood pressure to standing, Response of blood pressure to sustained hand grip, Bellavere's Scoring System was used to categorize the patients. The patients were categorized as normal, if all of the above tests were found normal. Early parasympathetic dysfunction was identified, in case of only one of the three tests of parasympathetic function came out to be abnormal. Definite parasympathetic dysfunction was identified, if two or more of the three tests of parasympathetic function came out to be abnormal. Sympathetic dysfunction alone does not exist, but instead combined damage occurs. The patients were having combined damage, if one or both sympathetic function tests were abnormal in addition to early or definite parasympathetic damage. The extent of the autonomic

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nervous damage was assessed by the CAN scoring system. For each test "0" score was given for normal test result, "1" was given for a borderline value of the test result and "2" for abnormal test result. For every subject, the total autonomic function score was calculated with addition the score of each of the five standard tests.

Statistical Analysis

In statistical analysis, the descriptive data was expressed as mean ± standard deviation. An independent 't' test was used to compare the Parasympathetic (Vagal) and sympathetic activity between the two groups. The analysis of the data was performed with SPSS 21. Gender was the qualitative variable used in the study and was presented as percentages. Quantitative variables of the study were age, blood pressure and all the laboratory findings including Serum creatinine, BUN, S. Alb, serum total protein levels, serum uric acid, fasting lipid profile, fasting blood glucose level, haemoglobin, TLC, Platelets, INR, ESR, serum sodium, serum potassium, calcium, ALT, AST and Alk. PO4, serum ammonia, total protein, serum albumin, direct bilirubin, total bilirubin, Free T4, and TSH. The quantitative variables were calculated with the help of a formula that is Mean± Standard Deviation t-test was used for comparison; it was significant as $p \leq 0.05$. The null hypothesis was rejected when $P < 0.05$.

RESULTS:

Patient Demographics

This study included 120 adults aged between 21-80 years, who visited the Mufti Mahmood Memorial Teaching Hospital Outdoor or indoor Patient Department, Dera Ismail Khan. There were 33 males (55%) in diabetic cirrhotic patients. Male to female ratio of diabetic cirrhotic patients was 1.2:1. There were 31 males (51.7%) with male to female ratio 1.1:1 in non-diabetic cirrhotic patients (Table 2, Figure 1). The gender distribution in the two groups is nearly same. Patients were divided into three age groups. Among diabetic cirrhotics in first age group, number of patients age between 21-40 years were 4 (6.7%), in second age group, patients age between 41-60 years were 34 (56.7%) and in the third group, patients age between 61-80 years were 22 (36.6%). The mean age was 57.48 ± 10.80 years. Whereas in the non-diabetic cirrhotics, in first age group, number of patients age between 21-40 years were 16 (26.7%), in second age group between 41-60 years were 25 (41.7%) and in the third age group between 61-80 years were 19 (31.6%) with mean age 51.92 ± 14.21 years. Statistically the difference between the groups was significant with $p < 0.01$ (Table 1).

Complications of Cirrhosis

Twenty-eight (46.7%) patients had history of variceal bleed in diabetic cirrhotic and 23 (38.3%) in non-diabetic cirrhotic group. Thus, incidence of variceal bleed is nonsignificantly higher in diabetic cirrhotic $p < 0.3$ (Table 1).

Autonomic Function Tests

Table 4 summarizes the signs and symptoms of chronic liver disease (primary eligibility criteria of selected patients) and cardiac autonomic neuropathy. Orthostatic hypotension is the most common symptom related specifically to cardiac autonomic neuropathy. The differences were non-significant all with p-values >0.05. The only difference which can be considered clinically significant was for orthostatic hypotension with p-value 0.065, it is near to 0.01.

Biochemical Profiles

Table 3 showed the mean ± standard deviations and the p-values of laboratory investigations of diabetic cirrhotic and non-diabetic cirrhotic patients. The differences were significant for Serum potassium, alkaline phosphate, Free T4 and TSH with p-value <0.025, <0.001, <0.019 and <0.001 respectively. Serum ammonia could be considered clinically significant with $p < 0.081$. Table 4 shows the autonomic function tests amongst diabetic cirrhotic and non-diabetic cirrhotic patients. In diabetic cirrhotic patients' para-sympathetic dysfunction, heart rate response to valsavla maneuver was found normal in 4 (6.7%), borderline 4 (6.7%) and abnormal 52 (86.6%), heart rate changes during excessive breathing was screened normal in 2 (3.4%), borderline 10 (16.6%) and abnormal 48 (80%) and immediate heart rate response to standing was found normal in 5 (8.3%), borderline 4 (6.7%) and abnormal 51 (85%). In diabetic cirrhotic patient's sympathetic dysfunction, blood pressure response to standing normal in 1 (1.7%), borderline 10 (16.6%) and abnormal 49 (81.7%) and response of blood pressure due to sustained hand grip, normal in 5 (8.3%), borderline 5 (8.3%) and abnormal 50 (83.4%). In non-diabetic cirrhotic patients' para-sympathetic dysfunction, heart rate response to valsavla maneuver was found normal in 4 (6.7%), borderline 8 (13.4%) and abnormal 48 (80%), heart rate changes during excessive breathing was screened out normal in 5 (8.3%), borderline 8 (13.4%) and abnormal 47 (78.3%) and immediate heart rate response to standing was found normal in 7 (11.7%), borderline 8 (13.4%) and abnormal 45 (75%). In non-diabetic cirrhotic patients' sympathetic dysfunction, blood pressure response to standing normal in 8 (13.4%), borderline 5 (8.3%), and abnormal 47 (78.3%) and blood pressure response to sustained hand grip, normal 12 (20%), borderline 2 (3.4%) and abnormal 46 (76.6%). The association of all these autonomic functions was statistically not significant. Blood pressure response to standing can be considered as, may be clinically significant, as $p < 0.019$.

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Parameters	Parameter's detail	Diabetic Cirrhotic (n=60)		Non-Diabetic Cirrhotic (n=60)	
		No.	%	No.	%
Gender wise distribution	Male	33	55	31	51.7
	Females	27	45	29	49.3
	Male to Female ratio	1.2:1		1.1:1	
Age group (Years)	21-40	04	6.7	16	26.7
	41-60	34	56.7	25	41.7
	61-80	22	36.6	19	31.6
	Mean ± SD	57.48 ± 10.80		51.92 ± 14.21	
History of Variceal Bleed	Yes	28	46.7	23	38.3
	No	32	53.3	37	61.7

Table 1: Demographic detail of the participants and their status

Signs & Symptoms	Diabetic cirrho		Non-diabetic cirrhoti		
	No.	%	No.	%	P-value
Jaundice	5	8.4	7	11.7	0.547
Anemia	15	25.00	10	16.7	0.261
Edema	20	33.4	15	25.0	0.310
Cyanosis	_	-	-	-	-
Palmar erythema	7	11.7	10	16.7	0.428
Finger clubbing	_	-	-	-	-
Dehydration	_	-	-	-	-
Orthostatic hypotension	35	58.3	25	41.7	0.065
Palpable lymph nodes	_	-	-	-	-
Spider naevi	4	6.7	7	11.7	0.342
Dupuytren contracture	_	-	-	-	-
Muscle wasting	_	-	-	-	-
Gynecomastia	12	20.0	15	25.00	0.511
Testicular atrophy	_	-	-	-	-
Hepatic Flap	2	3.3	1	1.7	0.574
Fetor hepaticus	26	43.4	21	35.00	0.344
Erectile dysfunction	35	58.4	30	50.0	0.354
Infectious diarrhea	_	-	-	-	-
Able to perform Star test	60	100.0	60	100.0	-
Resting heart rate	60	100.0	60	100.0	-

Table 2: Sign and symptoms of Cirrhosis and cardiac autonomic neuropathy

Laboratory findings	Diabetic cirrhotic	Non-diabetic cirrhotic	t test	P value
	Mean ± SD	Mean ± SD		
Haemoglobin	10.82 ± 1.65	11.25 ± 1.56	1.456	0.149
Total leukocyte count	6.28 ± 2.51	6.98 ± 4.80	1.000	0.320
Platelets	166.80 ± 99.38	179.02 ± 96.50	0.683	0.496
Prothrombin time	2.08 ± 0.74	2.00 ± 0.78	0.599	0.551
Activated partial thrombin time	2.43 ± 0.79	2.28 ± 0.94	0.946	0.346
Erythrocyte sedimentation rate	40.68 ± 15.94	36.26 ± 13.0	1.616	0.109
Blood urea nitrogen	25.76 ± 11.58	24.86 ± 10.41	0.447	0.656
Serum creatinine	1.30 ± 0.44	1.18 ± 0.44	1.576	0.118
Serum sodium	139.80 ± 6.87	138.43 ± 15.21	0.634	0.527
Serum potassium	3.99 ± 0.49	3.79 ± 0.47	2.277	0.025*
Serum calcium	7.53 ± 1.39	7.68 ± 0.77	0.757	0.453
ALT	57.73 ± 17.44	61.58 ± 17.18	1.219	0.225
AST	80.35 ± 21.66	76.43 ± 18.83	1.057	0.293
Alkaline phosphate	152.53 ± 29.39	130.88 ± 30.52	3.958	<0.001**
Serum ammonia	31.98 ± 12.72	28.52 ± 8.45	1.758	0.081
Total protein	6.90 ± 0.89	6.62 ± 1.06	1.584	0.116
Serum albumin	3.67 ± 0.51	3.60 ± 0.55	0.700	0.485
Direct bilirubin	1.58 ± 0.72	1.63 ± 0.78	0.425	0.672
Indirect bilirubin	1.45 ± 0.61	3.05 ± 0.61	0.964	0.337
Free T4	0.80 ± 0.50	0.61 ± 0.32	2.381	0.019*
TSH	1.00 ± 0.81	3.10 ± 1.43	9.684	<0.001**
Ultrasound	14.54 ± 0.31	14.42 ± 0.88	1.005	0.318

Table 3: Biochemical Profile

TEST	Daibetic			Non Daibetic			Chi-square P-value
		Borderline	Abnormal	Normal	Borderline	Abnormal	
Parasympathetic							
Heart rate response to valsalva maneuver	4	4	52	4	8	48	0.468
Heart rate variation during deep breathing	2	10	48	5	8	47	0.458
Immediate heart rate response to standing	5	4	51	7	8	45	0.355
Sympathetic							
Blood pressure response to standing	1	10	49	8	5	47	0.019*
Blood pressure response to sustained hand grip	5	5	50	12	2	46	0.107

Table 4: Tests for cardiac autonomic neuropathy

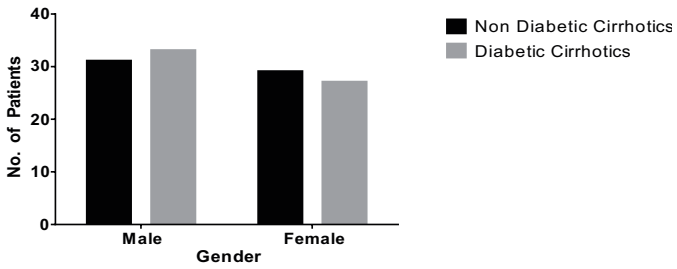

Figure 1: Gender distributions among two groups

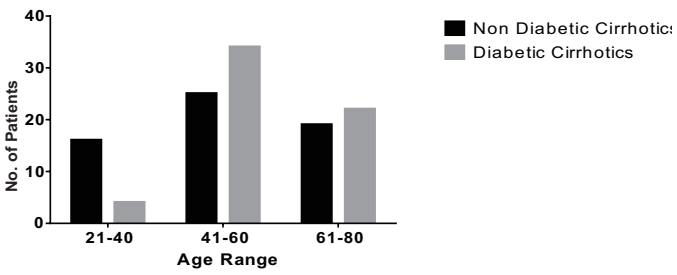

Figure 2: Age-wise distribution of Subject

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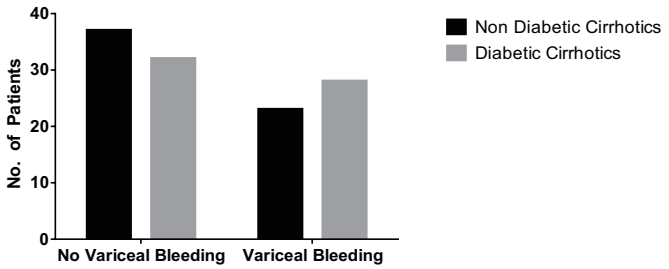

Figure 3: History of variceal bleeding among the patients

DISCUSSION:

Recent data suggests that liver cirrhosis is the 14th most frequent cause of mortality across the world with a 1-year mortality up to 57% [16]. The advancement in the liver abnormality makes the autonomic neuropathy even more worsen. Generally parasympathetic nervous system is affected earlier and more than sympathetic nervous system ANS dysfunction may be responsible for altered fluid homeostasis and neuro-humoral disturbances in cirrhosis [17,18]. Present study was conducted with the notion that comorbid diabetes would complicate a pre-existing autonomic dysfunction in the cirrhotic subjects. Different other variables were also considered for this purpose. Enrolled patients had fair gender distribution in both groups. Effect of gender was statistically insignificant (p-value > 0.05). This is also reported in other literature [19].

In terms of age, patients were normally distributed. However, diabetes had statistically higher incidence in more aged patients. Diabetes has strong, independent correlation with age [20]. Subjects in both groups were then evaluated for jaundice, anemia and edema. Although, those were manifested in both the groups, though the variation of occurrence of these signs was statistically non-significant. Same was the case with Palmar erythema, Orthostatic hypotension, Spider Naevi, Gynecomastia, hepatic flap, Fetor hepaticus, and erectile dysfunction. Other studies have also shown that symptoms like orthostatic hypotension can occur with nearly equal frequency in CLD patients with diabetes and CLD patients without diabetes [6].

Some parameters of biochemical and hematological profiles of both groups, on the other hand, showed some significant differences. Hematological profile was found to have no significant difference, with both groups registering similar hemoglobin load, TLC, platelets count, PT, APTT, and ESR. Hemoglobin was low, while TLC, platelets and ESR were border-line in both groups. Coagulation profile, marked by PT and APTT, was nearly equally deranged in both groups. Biochemical parameters like BUN, serum creatinine and serum electrolytes were near to reference ranges. There was statistically significant difference between serum potassium between both groups. Diabetics, in our study, had mild hyperkalemia. This phenomenon has already been documented previously [21]. ALT, AST were within reference ranges and almost the same between the groups. On the other hand, ALP was higher in both groups but significantly higher in diabetics. Higher levels of ALP have been reported in other literature [22], and this can mark the progression of the disease as well as poor prognosis in terms of cardiovascular health. Serum ammonia, albumin, and bilirubin was also within range in both groups. TFT showed hyperthyroidism in diabetics. As it has been summed up in a recent review article [23], diabetics can have a dysregulated thyroid profile, with most of the patients tilting towards hypothyroidism on account of low BMR.

In present study, high ratio of autonomic dysfunction was observed in the subjects of both groups that is diabetic cirrhotics and non-diabetic cirrhotics. Sympathetic function tests were found deranged in Fifty patients(83.4%), whereas parasympathetic function tests were found deranged in fifty-two patients (86.7%). The sensitivity of para sympathetic tests based on variation of heart rate is much higher than the sympathetic tests based on variation in blood pressure, in detecting the autonomic defects. In this study, it was concluded that the response of heart rate to standing was abnormal in remarkably higher frequency of subjects that is 51 out of 60 cirrhotic patients. Same study results were found by Barter and Tanner, who reported that the response of heart rate to standing was highly specific test and the most sensitive [24]. In contrary, Thuluvath and Triger quoted that the most sensitive test was the response of heart rate to deep breathing [25]. This test depends much on the cooperation of the subject and subject was instructed first about the procedure, and the subject may not follow us properly thus not easily manageable as compared to the response of heart rate to standing. Gentile et al quoted in their study that accuracy of deep breathing test and handgrip test depends upon the compliance of the patient, as the poor compliance affects the results badly [26]. In their study, they found the response of heart rate to deep breathing test and response of heart rate to standing tests were having most variations and are the most sensitive and specific tests respectively.

Overall, 120 patients studied had autonomic neuropathy, 2 or more abnormal tests – suggesting significant association between diabetic cirrhotic and non-diabetic cirrhotic and autonomic neuropathy. Eighty-seven percent of the patients with autonomic neuropathy belonged to CLD. Parasympathetic nervous system was affected more than sympathetic autonomic nervous system. In the diabetic cirrhotic group, 52 patients had parasympathetic tests derangement and 50 patients had sympathetic tests derangement. In non-diabetic cirrhotic 48 patients had parasympathetic tests derangement and 47 patients had sympathetic test derangement. After analysing the results

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of frequency of cardiovascular autonomic neuropathy, the comparison between the two groups reveals that there is no significant difference between the two groups.

CONCLUSIONS:

According to the findings of this study, comorbid diabetes didn't drastically affect autonomic function in cirrhotic patients. However, in certain biochemical markers showed some difference like alkaline phosphatase and TSH. These differences may be considered as the aberrant metabolic profile due to comorbid diabetes. Cardiac autonomic neuropathy found frequently in cirrhotic patient suggests that liver dysfunction contributes to the neurological deficit.

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