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Association of Heart Rate Variability with degree of Liver Fibrosis in Non-Alcoholic Fatty Liver Disease Patients

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ABSTRACT

Introduction: Progression of Non-alcoholic fatty liver disease (NAFLD) leads to development of non-alcoholic steatohepatitis (NASH) with increasing grades of fibrosis. NASH fibrosis has also been linked to increased incidence of death due to cardiac causes, usually sudden death. Cardiac autonomic dysfunction is now a known factor for sudden cardiac death. Heart rate variability (HRV) is a standard method of assessing cardiac autonomic function This study was performed to determine the association between HRV parameters and severity of liver fibrosis in NAFLD patients.

Methods: We recruited 82 ultrasonography diagnosed NAFLD patients in this cross-sectional study. They underwent transient elastography with FibroScan machine for evaluating the severity of their liver stiffness measure (LSM). On basis of LSM score these NAFLD patients were divided into 3 groups – NAFLD patients with no fibrosis (n=40), with significant fibrosis (n=23) and those with advanced fibrosis(n=19). All patients also underwent a short term 5-minute HRV assessment. Anthropometric tests and certain biochemical parameters were also performed and analysed in all 3 groups.

Results: In HRV, a significant increase was found in Heart Rate and a significant decrease in RR interval found to be associated with increase in severity of liver fibrosis. The median values of root mean square of successive differences (RMSSD), NN50 and pNN50%, high frequency (HF) and normalized HF, all measures of cardiac parasympathetic activity were decreased (though not significantly) in patients of NAFLD with significant and advanced fibrosis. However, measures of sympathetic activity like Low frequency (LF) and normalized low frequency (LF norm) as well as LF/HF ratio (marker of sympatho-vagal balance) displayed a rise (though not significant) with increase in severity of liver fibrosis. Anthropometric measures of weight, BMI and waist circumference (WC) were significantly increased with increase in severity of liver fibrosis.

Conclusion: We concluded that increased Heart Rate signifying a high sympathetic and low parasympathetic activity was positively associated and RR intervals were negatively associated with increase in severity of liver fibrosis in NAFLD patients. We also concluded that anthropometric measures of weight, BMI and WC were significantly associated with increase in severity of liver fibrosis.

Key words: ANS, Autonomic Nervous System; BMI, Body Mass Index; HRV, Heart Rate Variability; HTN, hypertension; IHD, ischemic heart disease; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-Alcoholic Steatohepatitis; WC, Waist Circumference; ANOVA, Analysis of Variance;

INTRODUCTION

Non- Alcoholic fatty liver disease [NAFLD] is a highly prevalent chronic liver disease which develops due to excessive lipid deposition in the liver without significant alcohol intake [1]. Significant intake is considered when there is history of consuming more than 21 doses of alcohol per week by males and more than 14 doses per week in women.[2] Another study considered >30gm/day for men and >20gm/day for women of alcohol intake as significant. [3] Simple liver steatosis with improper management could progress to non-alcoholic steatohepatitis (NASH) with varying grades of liver fibrosis culminating in cirrhosis or hepatocellular carcinoma.[4] Transient elastography measured by FIBROSCAN is a low cost, non-invasive test, acceptable test in clinical practice for diagnosing and quantifying liver steatosis and fibrosis. [5,6]

Increase in liver fibrosis has been associated with increased mortality. It has been documented earlier that the patients of NAFLD usually die of extra hepatic causes, mainly from cardiovascular diseases [2,7]. Thus, it is important to evaluate cardiovascular risk factors in all NAFLD patients. It is already known that cardiac autonomic nervous system modulates heart rate and blood pressure. The presence of cardiac autonomic dysfunction could predispose individuals to arrhythmias, hypertension (HTN), ischemic heart disease (IHD) and increased cardiac mortality in NAFLD patients. [8, 9] Sudden cardiac death, which has been linked to cardiac autonomic dysfunction, has been noted to be on the rise in NAFLD patients. [10] It has been found that worsening of chronic liver disease is associated with cardiac autonomic dysfunction.[11]

Heart Rate Variability (HRV) has proved to be a standard non-invasive method for evaluating effect of Autonomic Nervous System (ANS) on cardiac function [12]. HRV is a measure of the variation in consecutive inter-beat intervals of the heart beats and reflects the balance between the sympathetic and parasympathetic nervous system. Previous studies have shown that, following myocardial infarction, HRV is a powerful prognostic indicator of arrhythmic events.[13] HRV could be used clinically to identify patients at risk of sudden cardiac death. [14] HRV is used widely to assess cardiac autonomic function, because of its non-invasiveness and high repeatability.

Previous studies have also shown association between hepatic steatosis in NAFLD and cardiac autonomic dysfunction. [8,15] But it has yet not been clearly demonstrated whether worsening of NAFLD/ development of liver fibrosis accentuates cardiac autonomic dysfunction. The precise mechanism underlying the association between cardiac autonomic dysfunction and severity of liver fibrosis in NAFLD patients is poorly understood till now, therefore the present study was planned to find the association between cardiac autonomic function measured by HRV and degree of liver fibrosis in NAFLD patients.

MATERIAL & METHODS

The present study was executed in Physiology department of King George Medical University (KGMU), Lucknow from April 2023 to March 2024. Ethical approval was obtained by the Institutional Ethics Committee of KGMU, Lucknow. The subjects were enrolled from Gastroenterology OPD. Participants gave their informed consent after we explained to them the details like purpose, benefits and risks of the study. This was a cross-sectional study with a sample size of 80 (as per the prevalence of NASH being 5.5%.[8]

Ultrasonologically diagnosed 82 Patients of NAFLD of age 18 to 75 years were recruited from Gastroenterology OPD. Patients with history of significant alcohol consumption, suffering from Hepatitis B, C and HIV, those with endocrine disorders, chronic renal diseases, hereditary liver disorders, active malignancy, psychiatric disorders, pregnancy and lactation were excluded. Those with established diabetes mellitus, hypertension or cardiovascular diseases of > 5 years, were also excluded from the study.

Study Procedure:
A total 82 subjects (58 male and 24 females) with NAFLD were recruited for the present study. Transient Elastography of liver was done with FIBROSCAN mini + 430 by ECHOSENS on all these subjects on empty stomach with M or XL probe as appropriate. We took recordings of the controlled attenuation parameter (CAP) for liver steatosis and liver stiffness measure (LSM) for estimating liver fibrosis. The LSM values of all subjects were recorded in kilo Pascals (kPa). Based on the LSM values, the grading of fibrosis as per Echosens FibroScan machine and an earlier study was: F0-F1 (<7 kPa), F2 (7 TO 8.7 kPa) and F3(8.7 to 10.3 kPa) and F4 (> 10.3 kPa). [5]
The 82 subjects were categorized as per their kPa value into three groups :-
Group 1: NAFLD with Insignificant/no fibrosis with <7 kPa (F0-F1); n =40
Group 2: NAFLD with Significant fibrosis with 7 – 8.7 kPa (F2); n = 23
Group 3: NAFLD with Advanced fibrosis with > 8.7 kPa (F3-F4); n = 19

Anthropometric Measurements:
A detailed clinical history was taken and clinical examination was done of all patients. Height was measured by a stadiometer with the patient standing erect. The weight was measured on a digital scale with the weight equally distributed on both legs. Waist circumference was measured at the midpoint of line joining the top of iliac crest and the lowest tip of the lowermost rib. BMI is calculated as Weight (in Kg) /Height (m^2)

Heart Rate Variability (HRV) Assessment:
The status of cardiac autonomic function was estimated by assessing HRV in the ANS Laboratory of Physiology department of KGMU using Kody's Cardiac Autonomic Neuropathy (CAN) Analyzer Machine. The subject had to lie down on a couch with lead II ECG electrodes attached. The subject was asked not to move during collection of HRV data so that smooth recording without artefacts could be taken. HRV recording was done in a room with pleasant temperature between 22 to 25°C. A 5 min rest was given to the subject before the recording. Using CAN machine, a 5-minute lead II ECG was taken. This was recorded and analysed by the inbuilt Kody's software. HRV was performed in both Time domain and Frequency domain indices as recommended by the standards for HRV. The time domain indices of HRV computed were RR intervals, mean Heart Rate, SDNN, RMSSD, NN50 count and pNN50%. In frequency domain, the indices computed were Total Power, Low Frequency component (LF), High Frequency component (HF) along with their normalized units and the LF/HF ratio.

Biochemical Measurements:
Biochemical tests performed were Serum Total cholesterol, Serum Triglyceride, HDL, HbA1c, LDL, AST, ALT, viral markers (for Hepatitis B, C and HIV).

Statistical tools:
Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean and SD. Median with interquartile range was used for skewed (HRV) data. Quantitative variables were compared using one way ANOVA test / Kruskal Wallis test as appropriate among three groups. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done

using Statistical Package for Social Sciences (SPSS) version 23.0.

OBSERVATION AND RESULTS

The subject distribution in the 3 groups were as per Diagram1.

Anthropometric Measurements and General Characteristics: Table 1 shows that there was no significant relationship between age and severity of liver fibrosis. Whereas weight ($p<0.001$), BMI ($p=0.034$) and waist circumference($p=0.009$) were higher in NAFLD patients with significant and advanced fibrosis than in those with no fibrosis. Height, Hip circumference and waist-hip ratio did not show significant differences. There was a rise in systolic and diastolic BP with development of advanced fibrosis, but this was not significant enough. There was a significant rise in pulse rate ($p=0.30$) in NAFLD patients with significant fibrosis (86.83 ± 14.21) and a further rise in those with advanced fibrosis (91.16 ± 12.45) compared to those with no fibrosis (82.30 ± 10.25).

Biochemical Measurements: Table 2 shows that no significant changes were found in various lipid profile parameters and liver enzymes with severity of liver fibrosis. However, the Fasting blood sugar and HbA1C did exhibit a definite rise in the advanced fibrosis group compared to no fibrosis or even significant fibrosis. However, this rise was not statistically significant enough.

Heart Rate Variability: Table 3 displays the relationship between time and frequency domains of heart rate variability and the severity of liver fibrosis. Significant increase found in Heart Rate and a significant decrease in RR interval found to be associated with increase in severity of liver fibrosis. The median values of overall variability as computed by SDNN in time domain and Total Power in frequency domain demonstrated a decrease as the severity of liver fibrosis increased. This fall was considerable though statistically not significant. The RMSSD, NN50 and pNN50% which is a measure of cardiac parasympathetic activity exhibited a fall in patients of NAFLD with significant and advanced fibrosis. Similarly median values of other parasympathetic indicators like High frequency (HF) and normalized high frequency (HF norm), exhibited a decrease with increase in liver fibrosis severity. However, these levels were not found significant enough. Low frequency (LF) and normalized Low frequency (LF norm) both of which are measures of cardiac sympathetic tone displayed a rise with increase in severity of liver fibrosis in NAFLD patients. On the other hand, the LF/HF ratio, signifying the sympatho-vagal balance displayed a rise (though insignificant) with increase in severity of liver fibrosis.

Table 1: Anthropometry and General parameters of the subjects

	Groups as per severity of Liver Fibrosis								**p-value**
	Insignificant or No Fibrosis (F0-F1)		**Significant Fibrosis (F2)**		**Advanced Fibrosis (F3-F4)**		**Total Group**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (years)	41.55	10.25	38.26	10.38	43.11	13.65	40.99	11.16	**0.**354
Weight (kg)	72.02	8.88	81.83	10.01	79.37	10.53	76.48	10.47	**<0.001**
Height (cm)	161.95	7.52	166.00	8.68	163.68	7.04	163.49	7.86	0.143
BMI (kg/m^2)	27.54	3.58	29.75	3.61	29.71	4.19	28.66	3.85	**0.034**
Waist Circumference	99.25	7.80	106.09	10.13	104.42	9.14	102.37	9.24	**0.009**
Hip Circumference	102.40	8.55	106.83	10.25	104.18	7.26	104.05	8.89	0.164
Waist Hip Ratio	.97	.05	.99	.05	1.00	.05	.99	.06	0.092
Systolic BP	125.45	15.71	126.57	13.76	133.63	14.71	127.66	15.15	0.141
Diastolic BP	83.30	9.84	83.65	11.19	87.05	10.95	84.27	10.47	0.419
Pulse Rate	82.30	10.25	86.83	14.21	91.16	12.45	85.62	12.37	**0.030**

Applied one way ANOVA

Table 2: Biochemical Parameters of all subjects

	Groups as per severity of Liver Fibrosis								
	Insignificant or No Fibrosis (F0-F1)		Significant Fibrosis (F2)		Advanced Fibrosis (F3-F4)		Total Group		p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
FBS	104.90	29.82	103.86	13.66	114.30	29.29	106.79	26.21	0.362
HBA1C	6.60	1.80	5.48	.44	7.84	1.32	6.63	1.66	0.073
S. Cholesterol	170.63	37.28	185.57	35.68	168.42	41.76	174.31	38.12	0.245
S. Triglycerides	169.94	78.62	180.89	74.52	152.76	71.50	169.03	75.65	0.490
Serum HDL	47.50	12.56	46.47	7.17	43.74	18.87	46.34	13.09	0.592
LDL	97.97	33.79	99.76	28.22	89.32	28.62	96.47	31.05	0.512
VLDL	32.16	21.82	32.99	17.25	29.30	15.12	31.73	19.05	0.810
LDL/HDL ratio	2.18	.76	2.19	.73	2.24	.73	2.20	.74	0.955
SGOT	50.70	23.21	43.27	15.96	59.71	37.24	50.70	25.91	0.123
SGPT	65.57	34.82	60.11	28.81	84.48	76.55	68.42	46.86	0.214
Serum Alkaline Phosphatase	238.64	73.19	245.13	71.39	242.16	67.40	241.28	70.57	0.940

Applied One-way ANOVA test for significance.

Table 3: Time and Frequency Domain Indices of HRV in all subjects

	Insignificant or no Fibrosis (F0-F1)	Significant Fibrosis (F2)	Advanced Fibrosis (F3-F4)	Chi-Square value	p-value
	Median (IQR)	Median (IQR)	Median (IQR)		
Mean RR (ms)	769.77 (696.86 - 827.29)	738.71 (677.13 - 919.19)	708.57 (618.35 - 780.42)	5.481	0.065
SDNN (ms)	42.13 (28.4 - 72.03)	40.14 (21.06 - 61.66)	31.93 (23.24 - 53.99)	2.385	0.303
Mean HR	78.24 (72.86 - 86.8)	83.59 (75.21 - 90.77)	85.07 (77.02 - 98.5)	6.014	**0.049**
RMSSD (ms)	42.42 (23.37 - 69.53)	29.79 (11.59 - 68.36)	29.3 (16.77 - 37.29)	3.699	0.157
NN50 (count)	27.5 (5 - 39)	12 (1 - 34)	8 (3 - 32)	2.815	0.245
pNN50 (%)	6.63 (1.15 - 10.66)	2.69 (0.21 - 8.52)	1.89 (0.56 - 9.47)	3.138	0.208
Total Power	1269.9 (489.07 - 2950.76)	1204.96 (694.89 - 2298.6)	969.6 (362.84 - 3527.85)	0.180	0.914
LF	260.84 (125.26 - 879.69)	332.7 (169.2 - 758.87)	326.59 (124.97 - 560.16)	0.385	0.825
HF	258.92 (75.18 - 921.9)	236.18 (28.82 - 949.42)	165.11 (52.2 - 761.35)	0.795	0.672
LF norm	55.43 (41.81 - 67.02)	57.11 (52.57 - 75.4)	64.47 (34.9 - 82.53)	2.011	0.366
HF Norm	44.56 (32.97 - 58.18)	42.89 (24.6 - 47.42)	33 (13.67 - 50.89)	3.320	0.190
LF/HF Ratio	1.24 (0.72 - 2.03)	1.33 (1.11 - 3.06)	1.81 (0.54 - 4.72)	2.035	0.362

Applied Kruskal Wallis test

Diagram 1: Distribution of subjects as per their LSM values

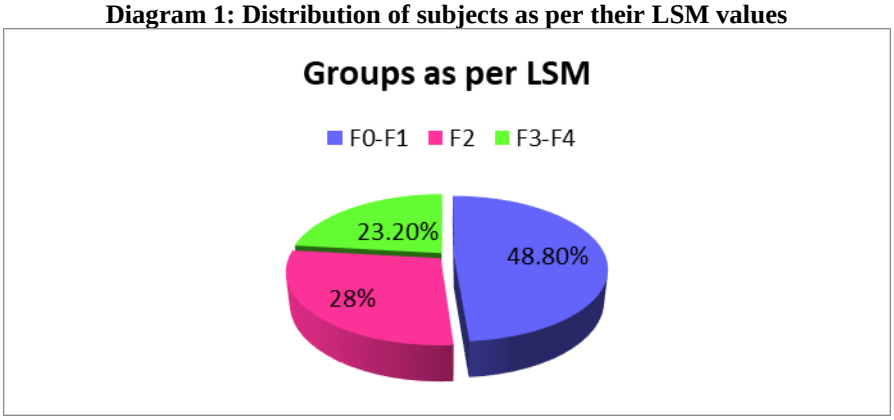


Diagram 2: Comparison of Anthropometric parameters of all 3 groups

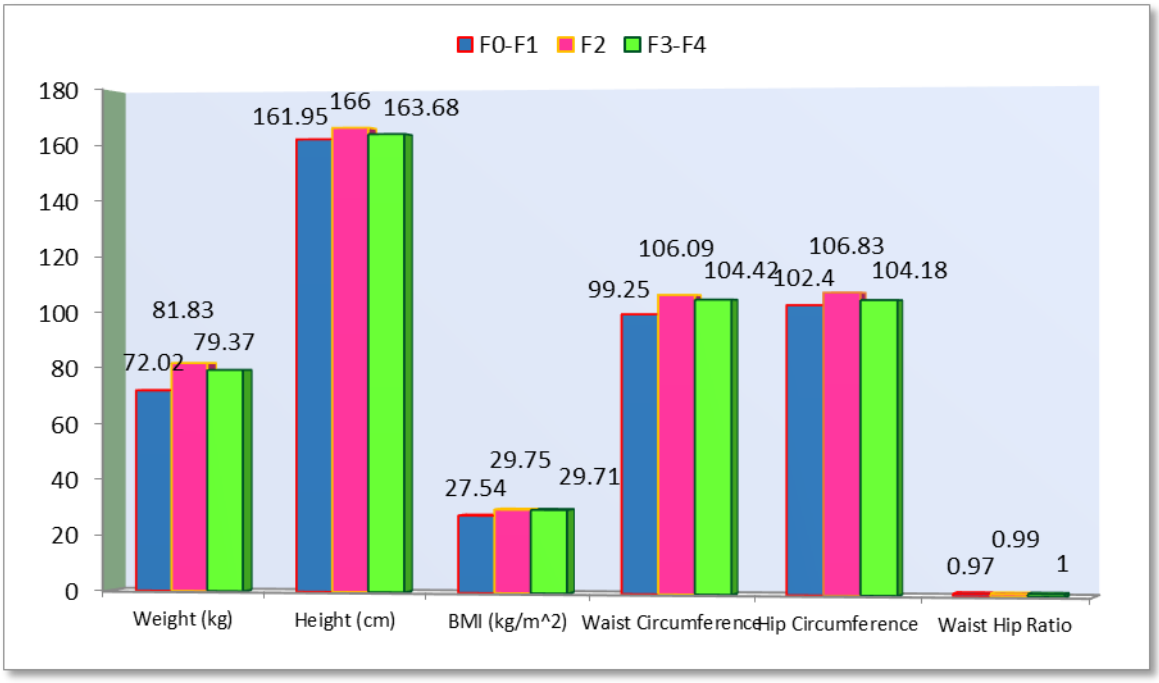
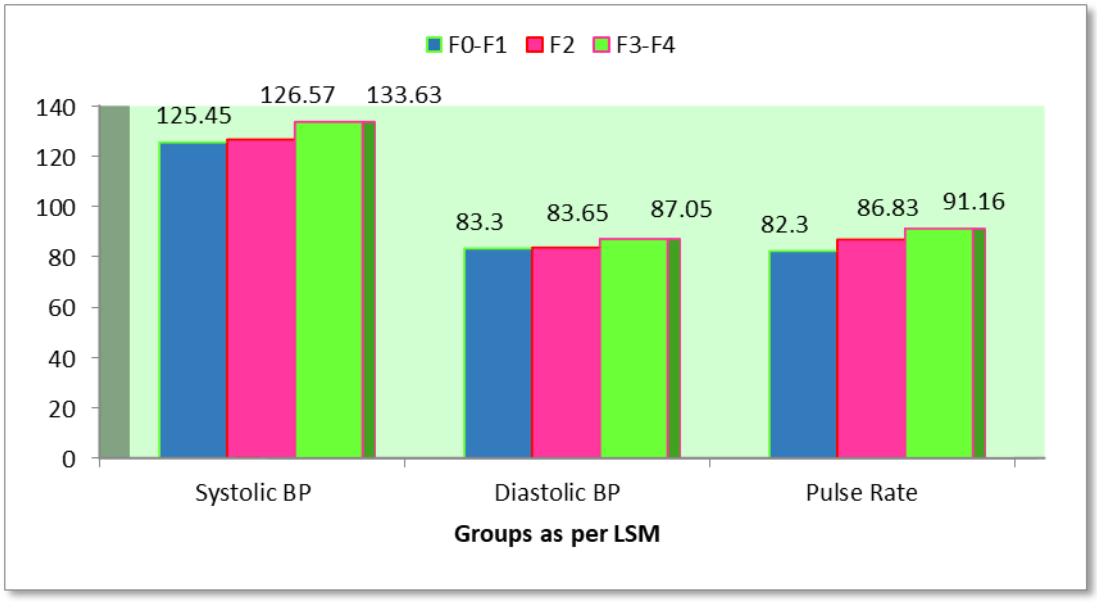


Diagram 3: Comparison of BP and Pulse Rate in all 3 groups



DISCUSSION

This study was done to assess the status of cardiac autonomic function (through HRV) of NAFLD patients with varying degrees of liver fibrosis and to find the association between the two.

Weight, BMI and waist circumference were significantly higher in NAFLD patients with significant and advanced fibrosis compared to those with no fibrosis. This could be due to the fact that as obesity increases, especially visceral obesity, it could worsen metabolic parameters of the body. In NAFLD patients if weight as well as visceral fat deposits increase further, it could lead to excessive fat deposits in the liver ultimately leading to hepatic inflammation with degeneration followed by fibrosis, a condition called NASH. Biochemical parameters of fasting blood sugar and HbA1C did show quite an increase in advanced fibrosis group as

compared to the other 2 groups. This rise could be explained on the basis that NAFLD is considered a metabolic disease and that the increase in visceral and liver fat is associated with insulin resistance. Our results exhibited a rise in systolic and diastolic BP with development of advanced fibrosis, but this was not significant enough. However, there was a definite rise in pulse rate in those with significant fibrosis and advanced fibrosis. This increased pulse rate could be due to sympathetic overactivity with increasing severity of liver fibrosis.

Similar findings were observed in HRV analysis. The indices of RR interval (which have reciprocal association with heart rate) exhibited a steady decline and the heart rate itself showed a definite rise with increase in degree of liver fibrosis. This may be explained on the basis that increased sympathetic activity (due to modern day stresses) leading to increase in basal heart rate could offset progression of NAFLD to NASH. However, the vice versa could also be true, i.e. the progression of NAFLD could lead to sympathetic overactivity with increased heart rate. Earlier studies too concluded that autonomic dysfunction with an overactive sympathetic tone could predispose an individual to development of NAFLD [15,16,17]. Inha Jung et al concluded that the development of NAFLD and liver fibrosis was associated specifically with a decreased parasympathetic activity and a recently increased sympathetic activity [3].

To support the above view, in our group even the values RMSSD, NN50 and pNN50%, HF and HF norm (all indices of cardiac parasympathetic activity) exhibited a fall in those NAFLD patients who had increasing levels of fibrosis. However as probably the group was small these values were not statistically significant. The median values of LF and LF norm (indices of sympathetic activity) displayed a rise (though not quite significant) with increasing levels of fibrosis. The LF/HF ratio, signifying the sympatho-vagal balance, displayed a rise (though insignificant) with increasing severity. Again, we reiterate that the autonomic dysfunction with increased sympathetic and reduced parasympathetic activity may be the trigger for disease progression from NAFLD with no fibrosis (i.e., pure NAFL) to NAFLD with significant fibrosis (i.e. NASH). In an earlier study by MMP Lira et al, the high frequency component, HF nu was found to be statistically associated in NAFLD patients with high risk of advanced fibrosis [18]. A study with 34,000 subjects concluded that a high sympathetic tone along with decreased parasympathetic activity could give rise to NAFLD [3]. Similarly, a cohort study also concluded that NAFLD was associated with an imbalance between the sympathetic and the parasympathetic tone as assessed by heart rate variability [8]. The median value of SDNN and Total Power signifying overall variabilities demonstrated a reasonable decline as the severity of liver fibrosis increased signifying overall compromised cardiac autonomic function with disease progression. In a previous study by Choi IY et al it has been observed that a low RMSSD and a low SDNN were independently associated significantly with development of incident hepatic steatosis and high risk of intermediate or advanced fibrosis based on FIB-4 or NFS scores. [19] As per earlier study activation of liver sympathetic nerves leads to worsening of liver fibrosis, while inhibition of sympathetic nerves reverses the liver fibrosis [20].

Clinical implication of this study is that autonomic dysfunction with decreased SDNN and RMSSD and decreased vagal activity may predispose a person to sudden cardiac death. This was in line with observation by Decker JM et al that increased cardiovascular mortality has been found to be associated with a lower SDNN value in HRV [21]. Secondly the knowledge that increased heart rate was consistently and significantly associated with increase in degree of liver fibrosis could be utilized as a

screening tool during follow up care of NAFLD patients.

Limitations of the study:
Since this was a cross- sectional observational study, the causal relationship between autonomic dysfunction and worsening of liver fibrosis in NAFLD could not be established. Additional prospective studies with a larger sample size are recommended to demonstrate these findings more accurately.

CONCLUSION

We conclude that increased levels of heart rate were consistently associated with worsening of liver fibrosis in NAFLD. Our study also demonstrated that the increase in degree of liver fibrosis was associated with increased sympathetic activity and a reduced parasympathetic activity. Our study re-establishes the fact that autonomic dysfunction with predominant sympathetic activity may be responsible for disease progression in NAFLD cases. It is important to diagnose NAFLD early and to prevent its progression to advanced fibrotic stages. Hence Weight, BMI, waist circumference, BP and pulse rate should be included in screening parameters and if possible, checked in every follow up visit. If these parameters show a significant rise the patient should be referred for Fibroscan assessment for identification of those at risk of advanced fibrosis.

Declaration by Authors

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