Original Article

Two faces of the same coin non alcoholic fatty liver disease; with and without diabetes: Comparative clinico pathological analysis: A cross sectional observational study

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Abstract

Background and Aim: Non-alcohol fatty liver disease (NAFLD) is a metabolic disorder that represents the hepatic manifestation of systemic process, and is a strong risk factor for diabetes Meletus, whereas the presence of DM increases the severity of NAFLD/NASH and its progression. Data on the impact of diabetes on NASH phenotype is sparse from northern India. We studied and compared the clinical profile of NALFD in the presence and absence of DM and the effect of diabetes on NASH. **Methods:** We did a cross-sectional analysis of data from NAFLD patients (n = 90) who were divided into diabetic and non-diabetic cohorts and their respective demographic, biochemical, imaging and histological features were recorded and compared. **Results:** Out of 90 patients, 53.3% were females with a mean age of 44 ± 12 years. The mean BMI and WHR of the study cohort were 28.9 ± 3.4 and 1.01 ± 0.15, respectively. The current study showed that 35.8% were diabetics. The mean age and WHR were 52 ± 11 years vs 40 ± 10 years and 1.1 ± 0.17 vs 0.99 ± 0.09, respectively, in diabetic and non-diabetic NAFLD patients. Non-invasive fibrosis scores, including BARD (2.8 vs 1.73), FIB-4 (3.4 vs 2.2) and NFS (0.97 vs −1.13), were significantly higher in diabetic NAFLD compared to non-diabetic NAFLD ($P < 0.03$). The histological grade of steatosis and fibrosis as depicted by the mean NAS score (5.7 ± 1.2 vs 4.63 ± 0.8) was higher in diabetic NAFLD vs non-diabetic NAFLD; however, only the fibrosis stage was statistically significant between the groups ($P < 0.001$). **Conclusion:** Despite the small no of cases, we should conclude that there is a bidirectional relationship between NAFLD and DM where the progression of one increases the rate of progression of other. Diabetic patients have higher risk of NASH and hence increased risk of liver related mortality and should be screened early for NAFLD/NASH.

Keywords: Cirrhosis, diabetes mellitus, metabolic syndrome, NAFLD, NASH, non-alcoholic steatohepatitis

Introduction

Non-alcohol fatty liver disease (NAFLD) is an umbrella term, which includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC). NASH is truly a histological diagnosis defined as the necro-inflammatory activity of liver parenchyma in addition to fat deposition.[1] Non-alcoholic steatohepatitis is

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a disease which over a period of 11–15 years may progress to cirrhosis and its complications that include variceal bleed, ascites, hepatic encephalopathy and hepatocellular carcinoma.[2,3] NASH is considered a potential premalignant condition and can directly degenerate into HCC in the absence of cirrhosis. NAFLD has recently evolved as a predominant cause of liver disease worldwide and is a major cause of what was previously known as cryptogenic cirrhosis.[4] The global prevalence of NAFLD is estimated to be 24% at present, with the highest rates in South America (31%), followed by Asia (27%), USA (24%) and Europe (23%).[5] The prevalence of diabetes is estimated to be 8.5% of the global population (WHO,2016). Among diabetic patients, 70−80% of patients have NAFLD. NASH may arise in the background of diabetes called as diabetic NASH, or in the absence of diabetes called as non-diabetic NASH.[6,7] The relationship between DM and NAFLD can be better understood by the concept of the common soil hypothesis, where the common trigger and perpetuator is insulin resistance (IR) that predisposes a normal liver to fatty degeneration and NASH. The association between the two is bidirectional.[4-8] DM is a well-established risk factor for the progression of NAFL to NASH and expands the risk of cirrhosis and HCC. On the other hand, NAFLD predisposes the individual for developing diabetes.[9–11] The current study is conducted to assess the clinical profile of NAFLD patients and compare the characteristics between diabetics and non-diabetics. This will also allow us to study the effect of diabetes on NAFLD phenotype and severity and vice versa.

Methodology

All patients with >18 years of age of either sex with a diagnosis of NAFLD who presented to gastroenterology OPD in Sher-I-Kashmir Institute of Medical Sciences, Srinagar J and K, India. The cases were enrolled from 2019 to 2022. NAFLD was diagnosed as per standard diagnostic criteria. Patients were included if they had evidence of fatty liver on recent (≤3 months before enrolment) ultrasound or other imaging modalities and absence of regular or excessive use of alcohol within 2 years prior to initial screening. Patients who were known cases of chronic liver disease, malignancy, rheumatological disease, thyroid dysfunction, coronary artery disease, chronic heart failure and chronic kidney disease were excluded. Patients were also excluded if they were on steroids, immunosuppressants, amiodarone, methotrexate and on any other drugs known to cause steatohepatitis. Patients with a history of recent surgery or who were on total parenteral nutrition were also excluded.

After meeting inclusion and exclusion criteria, patients' anthropometric data, blood investigations including haematological and biochemical variables, and histopathological parameters were recorded. All patients underwent liver biopsy and the classification given by Kleiner *et al.*[12] was used to grade and stage NAFLD/NASH (23). Grade of steatosis was defined: S0 = Steatosis less than 5%, S1 Steatosis means 5% to 33%, S2 Steatosis means 33–66%, S3 Steatosis >66%. Fibrosis was staged from 0 to 4: Stage 0 means absence of fibrosis; stage 1 means perisinusoidal or portal; stage 2 means perisinusoidal and portal/periportal; stage 3 means septal or bridging fibrosis; and stage 4 means cirrhosis. NAFLD activity score was calculated in each patient as the sum of the scores for steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2); which ranged from 0 to 8. Patients with an activity score of 5 or more were labelled as having NASH. The study cohort was divided into two groups as diabetic patients and non-diabetic patients and their different clinico-pathological parameters were recorded and compared. This study was approved by the Institutional ethical committee, and was conducted according to the guidelines in the Helsinki Declaration. Written informed consent was obtained from all patients.

Statistical analysis

The data was first keyed into a Microsoft Excel spreadsheet and cleaned for any inaccuracies. Data was expressed as mean ± standard deviation (SD), or as median with interquartile range (IQR), or percentage, whichever was appropriate for the subject's characteristic description. Group differences were compared using the Pearson Chi-square or Fisher's exact test for categorical variables, and the Student's *t* test or the Mann–Whitney U test for continuous variables.

Results

We prospectively analysed retrospective data of 90 patients in our study within a period of two years from March 2019 to November 2022 in our Department of Gastroenterology Sher-I-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India. The mean age of the study population was 44.68 ± 12.23 years among which 53.3% were females. The baseline characteristics, including anthropometric and blood variables, are given in Table 1.

Table 1: Baseline Characteristics of NAFLD Study Population

Parameter	*n*	Minimum	Maximum	Mean	Std. Deviation
Age	90	20	75	44.68	12.232
W/H ratio	90	0.8	1.8	1.0153	0.13032
Duration of detection	90	2	24	8.68	4.205
HB	90	7.89	17	12.871	2.06045
TLC	90	1.1	55	6.6014	5.63423
PLT	90	39	385	132.01	55.522
AST	90	10	192	66.79	39.41
ALT	90	16	403	89.16	73.44
ALB	90	3.46	5.01	4.0648	0.53009
INR	90	0.8	1.8	1.0961	0.16348
TG	90	68	865	214.79	118.033
CHO	90	108	300	185.13	39.865
LDL	90	35	183	103.26	28.523
HDL	90	28	119	42.18	13.753
NAS Score	90	2	6	4.76	1.02
BARD	90	0	4	2.09	1.196
FIB4	90	−2.12	12.1	2.6421	1.75751
NFS	90	−4.65	5.7	−0.4336	1.81751

In this current study, the mean BMI of the study population was 28.6 ± 4.9 and the mean waist/hip ratio was 1.02 ± 0.13. The percentage of overweight, obesity I and obesity II patients was 51%, 18% and 9%, respectively. Twenty-two percent (22%) patients were having normal BMI, and 82% of patients had central obesity. The percentage of diabetes, dyslipidaemia and hypertension was 35.8%, 54.4% and 16.7%, respectively, and 62% of patients fulfilled the criteria for metabolic syndrome.

As per our study aim, we compared the mean values of various parameters between two groups (non-diabetic NASH and NASH with diabetes) and the results obtained are given in Table 2.

The mean values of AST between non-diabetic and diabetic patients were 77.72 ± 41 and 44.9 ± 23, respectively, which were significantly different (95% C.I. 67.07–88.37 and 95% C.I. 36.03–53.83, $P < 0.001$). Similarly mean ALT values between non-diabetic and diabetic patients were 109.4 ± 80 and 48.5 ± 28, respectively, which were also significantly different (95% C.I. 88.68–130.29 and 95% C.I. 36.04–53.83, $P < 0.001$). The mean values for serum TGs were 223.6 ± 129 and 197 ± 89 in non-diabetic and diabetic patients, respectively (95% C.I. 190.18–257.16 and 95% C.I. 163.48–230.58, $P = 0.31$).

The mean values of various non-invasive composite fibrosis scores like FIB4, BARD and NFS were 2.80 ± 09, 3.4 ± 2.2 and 0.9 ± 2.0 (95% C.I. 2.57–4.25, 95% C.I. 2.45–3.15 and 95% C.I. 0.22–1.721, respectively) in diabetic NASH, and in non-diabetic NASH the respective scores were 1.73 ± 1.1, 2.2 ± 1.3 and −1.1 ± 1.2 (95% C.I. 1.9181–2.592, 95% C.I. 1.43–2.07 and −1.453–(−0.8206)), and the difference was statistically significant ($P < 0.003$) as shown in Table 3.

Between-group analysis, while comparing diabetic vs non-diabetic NASH in terms of severity of steatosis and fibrosis stage as shown in Tables 4 and 5, revealed that most of NASH patients with diabetes were having advance fibrosis (stages 3 and 4) compared to non-diabetic NASH patients, and the difference was statistically significant (70% vs 15%, $P = 0.001$). Severe steatosis was present in 43.3% of non-diabetic NASH, while 33.3% of diabetic NASH patients had severe steatosis. There was a trend towards higher steatosis grade in non-diabetic NASH when compared to diabetic NASH, but it did not reach statistically significant levels ($X^2 = 0.14$, $P = 0.93$). This is also reflected on the histopathology assessment score where diabetic individuals had a severe grade of liver disease as compared to non-diabetics as clearly depicted by mean NAS score 5.7 ± 1.2, 95% C.I. = 4.29–5.24 vs 4.63 ± 0.8, 95% C.I. = 4.54–4.97, $P < 0.94$) in diabetics vs non-diabetics, respectively; however, it did not reach statistically significant levels.

Discussion

There is not much data on NAFLD from India. Recent cognizance and interest in this disease, the presumably benign and non-progressive course of the illness, and the heavy burden of viral hepatitis might have led to a lower priority given to this disease and poor reporting of NAFLD from India. The aim to present this study is that we prioritize that diabetic individuals who are at high risk of fibrosis and progress rapidly to advanced liver disease as compared to the non-diabetic population, so before time assessment of fibrosis severity can identify at-risk individuals who are prone to develop advanced liver disease. Fibroscan, being a non-invasive tool for establishing liver disease and so diabetic individuals need early attention for screening of liver disease. Early detection of liver fibrosis is important in diabetics because it allows for early intervention and treatment to prevent further progression of liver damage.

Table 2: Comparison Of Baseline Variable Between Non-Diabetic and Diabetic NAFLD

Parameter		*n*	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	*P*
						Lower Bound	Upper Bound			
Age	No diabetes	60	40.9	10.942	1.413	38.07	43.73	20	60	≤0.001
	Diabetes	30	52.23	11.27	2.058	48.03	56.44	31	75	
	Total	90	44.68	12.232	1.289	42.12	47.24	20	75	
W/H ratio	No diabetes	60	0.9935	0.09559	0.0123	0.9688	1.0182	0.8	1.3	0.024
	Diabetes	30	1.059	0.17484	0.0319	0.9937	1.1243	0.88	1.8	
	Total	90	1.015	0.13032	0.0137	0.988	1.0426	0.8	1.8	
HB	No diabetes	60	13.47	1.84936	0.2387	12.9989	13.9544	9	17	≤0.001
	Diabetes	30	11.65	1.94783	0.3556	10.9323	12.387	7.89	15.5	
	Total	90	12.87	2.06045	0.2171	12.4394	13.3026	7.89	17	
AST	No diabetes	60	77.72	41.228	5.323	67.07	88.37	14	192	≤0.001
	Diabetes	30	44.93	23.814	4.348	36.04	53.83	10	106	
	Total	90	66.79	39.41	4.154	58.53	75.04	10	192	
ALT	No diabetes	60	109.4	80.533	10.39	88.68	130.29	17	403	≤0.001
	Diabetes	30	48.5	28.15	5.139	37.99	59.01	16	127	
	Total	90	89.2	73.44	7.74	74.03	104.37	16	403	
TG	No diabetes	60	223.6	129.64	16.73	190.18	257.16	68	865	0.31
	Diabetes	30	197	89.849	16.4	163.48	230.58	79	528	
	Total	90	214.7	118.03	12.44	190.07	239.51	68	865	

Table 3: Comparison of Non-Invasive Composite Scores and Histology Score Between Non-Diabetic and Diabetic NAFLD

Parameter		*n*	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max	*P*
						Lower Bound	Upper Bound			
BARD	No Diabetes	60	1.73	1.163	0.15	1.43	2.03	0	4	
	Diabetes	30	2.8	0.925	0.169	2.45	3.15	1	4	≤0.00 01
	Total	90	2.09	1.196	0.126	1.84	2.34	0	4	
FIB4	No diabetes	60	2.255	1.3059	0.1686	1.9181	2.5929	−2.12	7	
	Diabetes	30	3.415	2.2543	0.4115	2.5736	4.2571	0.9	12.1	0.003
	Total	90	2.642	1.7575	0.1852	2.274	3.01	−2.12	12.1	
NFS	No diabetes	60	−1.137	1.2248	0.1581	−1.4534	−0.821	−3.78	2.06	
	Diabetes	30	0.973	2.0035	0.3657	0.2252	1.7215	−4.65	5.7	≤0.00 01
	Total	90	0.434	1.8175	0.1915	−0.8142	−0.053	−4.65	5.7	
NAS score	No diabetes	60	4.65	0.876	0.113	4.52	4.98	2	6	
	Diabetes	30	5.77	1.278	0.233	4.29	5.24	2	6	0.94
	Total	90	4.76	1.02	0.108	4.54	4.97	2	6	

Table 4: Comparison of Steatosis Grading Between Non-Diabetic and Diabetic NAFLD

Steatosis		<5	5–33	34–66	Total
Diabetes	No	8	26	26	60
		61.50%	63.40%	66.70%	66.60%
	Yes	5	15	10	30
		38.50%	36.60%	33.30%	33.30%
Total		13	41	36	90
		100.00%	100.00%	100.00%	100.00%

In the current study, we registered 90 biopsy-proven NASH patients with a mean age of 44.68 ± 12 years reflecting a predominant surge of this disease after the fourth decade. In our study, females outnumbered males with the percentage of 53.3% of females and 46.7% of males, respectively. These findings are similar to the study conducted by Mcpherson *et al.*,[13,14] and Kühn *et al.*[15] However, our observations differ from the data recorded by Kumar *et al.*,[16] who studied 205 patients of NAFLD with a mean age of 40 years among which 70% were males. The exact reason for this gender distribution is not known.

We studied major risk factors of NAFLD such as obesity, HTN, dyslipidaemia and diabetes mellitus. The majority of our patients were either overweight (51%) or obese (18%). There were only two cases of extreme form of obesity (class 3 obesity per the Asian Pacific criteria with BMI >30) which is lower than the frequency of class 3 obesity described in Western data.[17] This data is similar to the data from the West, where NAFLD was found to be more common in obese individuals.[18,19] Similar results were obtained by Kühn *et al.*[15] and Halina Cichoż-Lach *et al.*[20] In this current study, 22% had normal BMI and this implies that NAFLD/NASH, although seen mostly in obese individuals, does not spare lean individuals and hence a recent concept of lean NASH has been introduced into the literature.

As NAFLD has an association with and is currently recognized as part of metabolic syndrome, we attempted to find out the various components of metabolic syndrome associated with NAFLD. Among our patients, 35.8% had diabetes mellitus, 54.4% had dyslipidaemia, and 16.7% were hypertensive. On subgroup analysis, DM was seen as most prevalent in the advanced age group (fifth decade and sixth decade). It is possible that diabetes mellitus occurs late in the course of this disease when the degree of insulin resistance increases and this accounts for increasing diabetes frequency in older age groups of NAFLD.

The current study revealed that in patients with diabetics, the NAFLD usually presents with advanced fibrosis at its initial diagnosis as depicted by mean values of various non-invasive composite fibrosis scores including FIB4, BARD and NFS. On histological assessment, diabetic patients had a severe grade of liver disease as shown by higher mean values of NAS score when compared to non-diabetics and the difference was statistically significant.

As definite diagnosis of NASH can be made only on histology, and liver biopsy is usually directed towards those with high-risk factors for significant liver disease, or where a specific answer is anticipated from liver biopsy such as ascertainment of the degree of inflammation and fibrosis or to determine long term prognosis. The results in our study depict that those patients who have advanced fibrosis on histology have higher mean values in terms of age, waist/hip ratio, BARD score and FIB4 score, and have lower mean values of AST, ALT, HB, PLT, NAFLD score and NAS score. By doing a comparison between our studied groups (diabetic vs non-diabetics), it was noted that diabetes significantly hand-out in fibrosis stage on liver histology; however, there was no significant difference in the amount of steatosis grade in individuals with diabetes as compared to non-diabetes. The results were similar to the study conducted by Hossain *et al.*[21] where diabetes was found an independent predictor of fibrosis in NAFLD.

The prevalence of non-alcoholic steatohepatitis (NASH) has been increasing rapidly and is at the forefront of worldwide concern. It has been well established that the presence of NAFLD/NASH increases the incidence of type 2 diabetes,

Table 5: Comparison of Fibrosis Stage Between Non-Diabetic and Diabetic NAFLD

Fibrosis Stage		0	1a	1b	1c	2	3	4	Total
Diabetes	No	16	13	5	8	9	7	2	60
		100.00%	92.90%	71.40%	100.00%	60.00%	31.80%	25%	66.60%
	Yes	0	1	2	0	6	15	6	30
		0.00%	7.10%	28.60%	0.00%	40.00%	68.20%	75%	33.30%
Total		16	14	7	8	15	22	8	90
		100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

while diabetes aggravates NAFLD to more severe forms of steatohepatitis, cirrhosis and hepatocellular carcinoma.[22-24] It is clear from previous data[25] and the present study that there is a complex bidirectional relationship between the progression of NASH and the development of T2DM, and their interaction could result in an increase in both hepatic and diabetic mortalities in patients with concomitant NASH and T2DM.

Limitation

The limitation of this study is the small sample size and the retrospective nature of the analysis. As the study is from a single centre, extrapolation and generalization of data to other populations cannot be made. The data needs replication from large perspective multicentre studies to validate the findings in practice.

Conclusion

Despite the small no of cases, we showed that there is a bidirectional relationship between NAFLD and DM where the progression of one increases the risk of progression of the other. Diabetic patients have a higher risk of NASH and progression to advanced liver disease, and hence increased risk of liver-related mortality and should be screened early for NAFLD/NASH.

Novelty of study:
The key message is that by identifying at-risk individuals at an early stage, appropriate management strategies can be implemented to reduce the risk of complications and improve overall outcomes in diabetics.

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Conflicts of interest

There are no conflicts of interest.

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