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Original Research Article

Study of Prevalence of Nonalcoholic Fatty Liver Disease [NAFLD] by Non Invasive Diagnostic Criteria in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH) are the most common causes of liver disease in western countries. Prevalence of NAFLD is increasing even in developing countries mainly due to the increasing numbers of people with obesity or with metabolic syndrome and type 2 Diabetes Mellitus.
Methods: A total of 50 type 2 Diabetes Mellitus (DM) patients were evaluated for detailed history, demographic profile, anthropometric measurements, microvascular complications of type 2 DM, routine blood investigations, and tests for current glycemic status (FBS, PP2BS, HbA1C). Patients underwent ultrasonography to detect NAFLD. Serum transaminses (ALT and AST) levels were measured in all patients and ratio of AST/ALT was calculated to see sensitivity and specificity of same in comparision to ultrasonography.
Result: NAFLD was found in 32 (64%) patients out of 50 patients of type 2 DM by ultrasonography. Obesity and dyslipidemia, two important components of metabolic syndrome were found to have statistically significant association with occurrence of NAFLD in type 2 DM patients (p value: <0.01). Most of the patients (87.5%) in NAFLD type 2 DM group were having diabetes for more than 5 years so it seems likely that long duration of diabetes is at higher risk to develop NAFLD. There was highly statistically significant inverse relation between metformin therapy and development of NAFLD, (p value:< 0.001). It was noted that uncontrolled HbA1C level has association with increase prevalence of NAFLD (93.75%). type 2 DM patients with microvascular complications are at increased risk of developing NAFLD (p <0.005). Increased ALT levels (Sensitivity 59.38%, and Specificity 94.44%) and AST/ALT ratio less than one (Sensitivity 96.87% and Specificity 77.78%) were observed more frequently in NAFLD patients as compared to AST (Sensitivity 0 and Specificity 100%), so increased ALT and AST/ALT ratio can be used as biochemical marker to detect chronic liver disease such as NAFLD.
Conclusion: High prevalence of NAFLD is seen in Indian type 2 DM population. In our study we demonstrated the association between elements of metabolic syndrome, duration of diabetes, increase HbA1C level and microvascular complications of diabetes mellitus with occurrence of NAFLD. Metformin therapy may have protective role in development of NAFLD especially in type 2 DM. Our study also highlighted importance of evaluation of aminotransferases level in type 2 DM, which can be used as marker for chronic liver disease, like NAFLD in type 2 DM.

Keywords: Type 2 Diabetes Mellitus, Non-alcoholic fatty liver disease (NAFLD).

INTRODUCTION

Non Alcoholic Fatty Liver disease (NAFLD) is becoming a major public health problem all over world. The prevalence of NAFLD has increased up to two times in last 20 years, whereas other chronic liver

diseases have same prevalence as before or even decreased. It is the most common liver disease in the United States and world-wide. Currently in general populations of United States, prevalence of NAFLD is around 20%. The prevalence in the morbidly obese population has been estimated as 75-92%, while that in the pediatric population, as 13-14%. [1] Prevalence of NAFLD is increasing in developing countries, mainly due to major lifestyle modifications. Epidemiological studies had suggested prevalence of NAFLD in general population o f India is around 9% to 32% with higher prevalence in those with overweight or obesity and those with diabetes or prediabetes. Published literature on NAFLD from India is spare may be because of condition was recently recognized, there was a presumption that the NAFLD is benign and has a non-progressive course, and a large burden of viral hepatitis in India tends to reduce the priority accorded to this condition. [2] This study is done to find out the prevalence of NAFLD in diabetes patients as well as to establish non-invasive cost effective diagnostic criteria for the same.

MATERIALS & METHODS

A cross section study was conducted at SBKS Medical Institute & Research Centre, Piparia, Waghodia after clearance from the institutional ethics committee. 50 adult patients of type 2 DM were enrolled, and those with history of chronic alcoholism, with chronic liver disease and patients on hepatotoxic drugs were excluded. Demographic profiles, detailed history, clinical examination including anthropometric measurements were noted. The NAFLD was diagnosed on basis of ultrasonography. Serum transaminases (ALT-Alanine Aminotransferase AST-Aspartate Aminotransferase) were also been measured in all patients and ratio of AST/ALT was also calculated in all patients (AST or ALT > 40 IU/L was considered as abnormal, and AST/ALT ratio <1 was considered abnormal finding to diagnose NAFLD). All the patients were subjected to RBS, PP2BS, and HbA1C level to know the current status of hyperglycemia. They were also evaluated for microvascular complications of type 2 DM. All this data was collected in CRF and was tabulated in Microsoft excel, further data analysis has been done using various appropriate statistical methods and results were prepared.

RESULT

The prevalence of NAFLD in type 2 diabetic patients in our study was 64%, with mean age of 58.66 ± 9.17 and male to female ratio was M:F=1.3:1. The metabolic syndrome risk factors hypertension, obesity, and dyslipidemia were more prevalent in NAFLD group than in Non-NAFLD group. (Table: 1)

Table 1: Demographic characteristics of study population and Association of NAFLD with components of metabolic syndrome and IHD.

		NAFLD		Total	p-value
		Present n=32 (64%)	Absent n=18 (36%)		
Age (years)	<35	1(3.12%)	0(0)	1(2.0%)	0.596
	35-50	6(18.75%)	2(11.11%)	8(16.0%)	
	50-70	23(71.87%)	13(72.22%)	36(72.0%)	
	>70	2(6.25%)	3(16.66%)	5(10.0%)	
Sex	Male	18(56.25%)	9(50%)	27(54.0%)	0.771
	Female	14(43.75%)	9(50%)	23(46.0%)	
HT		14(43.75%)	4(22.22%)	18(36.0%)	0.219
IHD		3(9.37%)	4(22.22%)	7(14.0%)	0.398
Obesity		17(53.13%)	1(5.55%)	18(36.0%)	0.002

Mean duration of DM was of 5.62 ± 2.07 years in study population. NAFLD type 2 DM group, had mean duration of 7.12 ± 2.80 years. And Non-NAFLD type 2 DM group had mean duration of 2.44 ± 1.51 (95% CI: 1.26 to 2.09, p <0.001). The

statistically significant association was found between increasing duration of DM and occurrence of NAFLD in our study. Out of 22 patients taking metformin for treatment of DM, only 6 (18.75%) patients had NAFLD, while out of 28 patients not taking metformin, 26 (81.25%) patients had NAFLD. This result suggests highly statistically significant inverse relation between metformin and development of NAFLD, as p value was less than 0.001. (Table: 2)

Only 6.25% patients of controlled HbA1C (<7.5%) had developed NAFLD while patients with mildly elevated HbA1C (7.5-9%), moderately elevated HbA1C (9-11%) and severely raised HbA1C (>11%) had developed NAFLD in 84.61%, 90.9%, 100% respectively (p value: <0.001). (Figure: 1) 78.13% of DM patients having retinopathy, 62.5% having neuropathy, 75% with nephropathy had NAFLD, showing statistically significant association between development of microvascular complications and NAFLD in type 2 DM.

The mean value of ALT in NAFLD group was 43.12 ± 10.457 and in Non NAFLD group was 26.94 ± 6.725 (95% CI: 10.667 to 21.694, p value <0.001), suggesting that patients with type 2 DM who are having NAFLD had increased level of ALT, as compared to Non NAFLD DM patients. Mean value of AST in NAFLD group was 23.91 ± 7.785, and in Non NAFLD group was 27.39 ± 5.564 (95% CI: -7.676 to 0.711, p value: 0.101) suggesting that there were no relation between NAFLD and elevation of AST in type 2 DM. (Table: 3)

Sensitivity of ALT to use as diagnostic marker for NAFLD in type 2 DM was 59.4% in the study, while it is 94.4% specific for the same. AST was highly specific but lack sensitivity, and Sensitivity of AST/ALT was 96.87% and specificity was 77.78%. (Table: 4)

Table 2: Association of duration of type 2 diabetes mellitus and Metformin therapy with development of NAFLD.

Duration of DM	NAFLD n=32 (64%)	Non-NAFLD n=18(36%)	P value
< 2 yrs.	2 (6.25%)	10 (55.55%)	<0.001
2-5 yrs.	2 (6.25%)	8 (44.44%)	
5-10 yrs.	18 (56.25%)	0 (0%)	
>10 yrs.	10 (31.25%)	0 (0%)	
Metformin			
Taking (n=22)	6 (18.75%)	16 (88.88%)	<0.001
Not taking (n=28)	26 (81.25%)	2 (11.11%)	

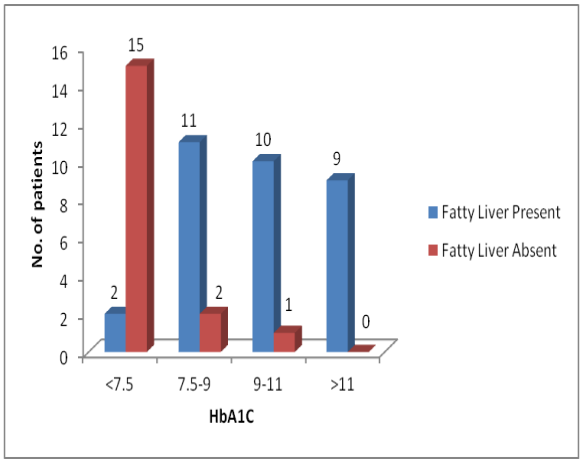

Figure 1: Association between NAFLD and severity of HbA1C.

Table3: Association between NAFLD and microvascular complications of type 2 DM and Liver enzymes.

Microvascular complications	NAFLD		p-value
	Present 32 (64%)	Absent 18 (36%)	
DM retinopathy(n=27)	25 (78.13%)	2 (11.11%)	<0.001
DM Neuropathy(n=22)	20 (62.5%)	2 (11.11%)	0.001
DM Nephropathy(n=30)	24 (75.0%)	6 (33.33%)	0.006

Table 4: Sensitivity and Specificity of liver enzymes for diagnosis of NAFLD

USG	ALT			AST			AST / ALT (Ratio)		
	Increased	Normal		Increased	Normal		Increased	Normal	
NAFLD (n=32)	19 (59.38%)	13 (40.62%)	Sensitivity 59.38%	0	32	Sensitivity 0%	31 (96.87%)	1 (3.12%)	Sensitivity 96.87%
Non NAFLD (n=18)	1 (5.55%)	17 (94.44%)	Specificity 94.44%	0	18	Specificity 100%	4 (22.22%)	14 (77.78%)	Specificity 77.78%

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) represents a continuum of disease, characterized histologically by excessive accumulation of hepatic fat in absence of significant alcohol consumption; with or without inflammation, varying degree of fibrosis, and cirrhosis. A number

of studies have found a positive relationship between hyperinsulinaemia, abnormal glucose tolerance, and NAFLD. Incidence of type 2 DM is increasing throughout the world, reaching levels of pandemic in countries like India and China. [3] Non Alcoholic fatty liver disease (NAFLD) is an emerging as the most common cause of chronic liver disease worldwide, probably related to the increasing incidence of obesity and type 2 DM. It is clearly an important public health issue but the magnitude of the problem of NAFLD in patients with type 2 diabetes mellitus is currently unknown. [4] Recently liver disease has been recognized as a major complication of type 2 DM with standard mortality rates for cirrhosis greater than that for cardiovascular disease. [5] The prevalence of NAFLD, as diagnosed by characteristic ultrasonographic features, in the type 2 diabetic populations was found to be very high. The diagnostic criterion used in all studies was ultrasonography. The overall prevalence of NAFLD in western countries varies from 15-40%. The prevalence rate of NAFLD falls between 55%-65% in all studies done in India. Our study results (64%) are in concordance with the studies done by AK Agrawal et al, M Prashanth et al, Somalwar AM et al. [6,7] It has been hypothesized by previous researcher that as the age increases, prevalence of NAFLD increases [8] which may be related to more prolonged diabetes. Most of the studies in India have shown higher prevalence of NAFLD in male than in female populations (M:F ratio of 2:1 approx.), [9,10] while Kalara S et al had found slightly higher prevalence rate of NAFLD in female (60%) than in male (54.3%) population. We could not able to find any significant gender preponderance.

It is known that NAFLD is an integral part of the metabolic syndrome which comprises a cluster of abnormalities such as dyslipidemia, hyperglycemia, hypertension, and obesity with insulin resistance as a central pathogenic factor. Some studies showed that significant number of patients with NAFLD also had elevated both systolic and diastolic blood pressure. [11,12] Similar results were observed in the present study but this observation was not significant statistically. But hypertension is a part of metabolic syndrome and metabolic syndrome has significant correlation with development of NAFLD, we should always check for blood pressure in patients who are at risk of developing NAFLD. The prevalence of NAFLD in type 2 DM has been consider as independent risk factor for coronary artery disease (CAD) by various researchers. [6,8] Obesity in particular central obesity has been described as one of the strongest risk factors for NAFLD and fibrosis, with NASH being prevalent in 18.5% of obese patients. [13] In our study 53.13% were obese with NAFLD, this results was in concordance with the various studies done by various researchers. [6,14,15] Dyslipidemia is also one of the factors which is associated with NAFLD as a component of metabolic syndrome. Wide range of prevalence (20%-90%) of dyslipidemia has been reported in patients with NAFLD, [16] we have noted prevalence of dyslipidemia was 90.6%. Hypertriglyceridemia or hypercholesterolemia or both were present in almost all patients. Difference in prevalence of dyslipidemia between both sub groups was statistically significant, which suggest that dyslipidemia in diabetes increases the risk of NAFLD. Almost all patients of type 2 DM who have dyslipidemia or obesity, they are at high risk of developing NAFLD and they must evaluate for NAFLD.

It was reported that the prevalence rate of NAFLD increases significantly with prolonged course of diabetes in study done by Somalwar et al.7 Insulin resistance is a part of pathogenesis in development of NAFLD; metformin is an insulin sensitizer so it might be having preventive potential in type 2 DM patients who are at high risk of developing NAFLD. Silverman JF et al. stated that Insulin sensitizer like metformin may have protective role in prevention and progression of NASH, Several studies investigated the effect of metformin on

aminotransferases and liver histology in patients with NASH. Early small, open-label studies demonstrated a reduction in insulin resistance and aminotransferases [17-19] but no significant improvement in liver histology. [18,19] It was reported by Somalwar AM et al that patients with uncontrolled diabetes or high HbA1C are at higher risk of developing NAFLD. [7] It is clearly demonstrated in our study that metformin therapy is inversely associated with development of NAFLD, only 18.75% patients on metformin developed NAFLD while 81.25% patients taking other therapy developed NAFLD. This statistically significant difference suggests that metformin has protective role in development and progression of NAFLD. It implies strict control of diabetes and regular monitoring of HbA1C is essential for prevention of NAFLD. We evaluated all patients for microvascular complications in type 2 DM, results were found to be very high (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy: 78.13%, 62.5% and 75% respectively) in my study, Somalwar AM et al noted similar results. [7] Recent study done by Targher et al. reported that NAFLD patients had higher age and sex adjusted prevalence of both retinopathy and nephropathy. [8] Our study suggests that development of NAFLD was strongly associated with higher prevalence of all three microvascular complications of type 2 DM. The results had shown high mean value of HbA1C in NAFLD patients as compared to Non-NAFLD patients.

Study done by Sanjay Kalra et al. had shown that mean ALT and AST levels in NAFLD group were higher than that of Non NAFLD group, ALT level were increased more than AST level. [20] ALT appears to have role in gluconeogenesis and seems to be more related to liver fat accumulation than AST. Similar results were obtained in my study. We also observed that mean values of both the transaminases are more in NAFLD group than in Non NAFLD group and ALT found to be more increased than AST. So our study suggest that increased levels of transaminases especially ALT and AST/ALT ratio can be used as biochemical markers to diagnosed chronic liver disease like NAFLD. Radio imaging (ultrasonography) is established as gold standard diagnostic modalities to detect NAFLD, which has sensitivity and specificity of 89% and 93% respectively in one study. [20] We have compared specificity and sensitivity of serum transaminases and AST/ALT ratio with ultrasonographic diagnosis with taking it as definitive diagnostic test. In our study AST/ALT ratio referred to be most sensitive (96.87%) followed by ALT for diagnosis of NAFLD, while elevated AST highly specific followed by ALT to diagnose NAFLD in comparison with ultrasonography. So our study suggests that serum ALT and AST/ALT ratio can be used as biochemical marker for diagnosis of NAFLD especially in type 2 DM

Limitations of the study:

A limitation of our study is that the diagnosis of NAFLD was based on ultrasonography and not by liver biopsy. Ultrasonography is by far the commonest method of diagnosing NAFLD in clinical practice and has very good sensitivity and specificity. The sensitivity and specificity of ultrasound for detecting hepatic steatosis varies from 60 to 94% and 88 to 95% respectively which suggest that liver biopsy seldom necessary to diagnose NAFLD as it is invasive method.

CONCLUSION

High prevalence of NAFLD in Indian type 2 DM population is now an established fact. In our study we demonstrated the association between elements of metabolic syndrome, duration of diabetes, increase HbA1C level and microvascular complications of diabetes mellitus with occurrence of NAFLD. Metformin therapy may have protective role in development of NAFLD especially in type 2 DM. Our study also highlighted importance of evaluation of aminotransfera-

ses level in type 2 DM, which can be used as marker for chronic liver disease, like NAFLD in type 2 DM.

Our study emphasize the need for frequent evaluation of aminotransferase levels in type 2 DM patients, as even mild elevation of these liver enzymes may be a sign of unanticipated hepatic disorder. We sincerely wish this study will be an important step in understanding prevalence and risk profile of NAFLD in Indian type 2 DM patients and designing preventive strategies.

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