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Original Research Article

NONALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS - AN INDEPENDENT PREDICTOR FOR MICROANGIOPATHY

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Abstract

Background: The incidence of NAFLD is higher in the diabetic population which may act as a predictor for diagnosis of micro and macrovasuclar disease. **Aim:** The aim is to assess whether nonalcoholic fatty liver disease is related to diabetic microangiopathy in patients with type 2 diabetes mellitus. **Materials and Methods:** Patients are selected from the Internal medicine department of SS Institute of Medical Sciences & Research Centre, Davangere. In patients with type 2 diabetes Mellitus, Fasting & postprandial glucose, lipid profile, liver function test with enzymes, Ultrasonogram, Urine spot albumin creatinine ratio, blood urea and creatinine will be done after obtaining written informed consent and the findings correlated to find out whether NAFLD is an independent predictor of angiopathy in these patients. Baseline ultrasound abdomen was done in all patients to look for fatty liver. The peripheral neuropathy in diabetic patients is diagnosed by testing the vibration sense and deep tendon reflex. The fundus examination is done with direct ophthalmoscope by which diabetic retinopathy is identified. **Result:** Out of 100 patients with diabetes 24 had retinopathy, 18 had peripheral neuropathy, 59 patients are in grade 1 diabetic nephropathy, 38 patients are in grade 2 diabetic nephropathy, 1 patient in grade 3 diabetic nephropathy and 2 patients in grade 4 diabetic nephropathy. Out of 40 patients with NAFLD 14 had retinopathy, 14 had peripheral neuropathy. Among NAFLD patients with diabetic nephropathy 24 patients are in grade 1 diabetic nephropathy, 15 patients are in grade 2 diabetic nephropathy and 1 patient in grade 3 and no patient in grade 4 nephropathy. The prevalence of retinopathy (14 Vs 10), peripheral neuropathy (14 Vs 4) is high among NAFLD group when compared to that of no NAFLD group all of which are statistically significant. **Conclusion:** The study concluded that diabetic patients with nonalcoholic liver disease had high prevalence of diabetic retinopathy, diabetic peripheral neuropathy, and did not have any relation with diabetic nephropathy.

INTRODUCTION

Nonalcoholic fatty liver disease is a condition in which there is collection of fat in liver cells mainly triglycerides. Fatty liver and excessive alcohol consumption are often associated. For the last two decades, fatty liver occurring in non-drinkers i.e. non-alcoholic fatty liver disease (NAFLD) has increased dramatically. Today, NAFLD is considered as one of the most common liver disease in the developed world. It has a strong assosciation with obesity, insulin resistance, and hypertension. Thus NAFLD can be considered as the hepatic manifestation of the metabolic syndrome. The severity of NAFLD increases with increasing number of components of metabolic syndrome.

The prevalence of the disease in Indian population is 15 to 20 %, whereas the prevalence among diabetes population is more than two fold higher (50 to 75%). The incidence of type 2 DM is increasing throughout the world, reaching levels of a pandemic in countries like India and China. Only recently has liver disease been recognized as a major complication of type 2 DM with standard mortality rates for cirrhosis greater than that for cardiovascular disease.

The risk factors for nonalcoholic fatty liver disease are morbid obesity, type 2 diabetes mellitus, older age (>50 years), insulin resistance, and hyperlipidemia. NAFLD has been associated with many conditions which has mitochondrial injury as a key pathogenic mechanism. The incidence of NAFLD is higher in the diabetic population which may act as a predictor for diagnosis of micro and

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macrovasuclar disease. The micro and macrovasuclar disease have a great impact on economy of the patient.

MATERIALS AND METHODS

Source of Data: Patients are selected from the Internal medicine department of SS Institute of Medical Sciences & Research Centre, Davangere.

Methods of Collection of Data:

This was a cross-sectional study conducted in SS Institute Of Medical Sciences & Research Centre, Davangere from Nov 2018 - Oct 2020. In patients with type 2 Diabetes Mellitus, Fasting & postprandial glucose, lipid profile, liver function test with enzymes, Ultrasonogram, Urine spot albumin creatinine ratio, blood urea and creatinine will be done after obtaining written informed consent and the findings correlated to find out whether NAFLD is an independent predictor of angiopathy in these patients.

Baseline ultrasound abdomen was done in all patients to look for fatty liver. The patients vibration senses are tested with 128 Hz turning fork. The peripheral neuropathy in diabetic patients is diagnosed by testing the vibration sense and deep tendon reflex. The fundus examination is done with direct ophthalmoscope by which diabetic retinopathy is identified. Diabetic nephropathy was staged according to analysis of the spot urine sample as:

DN stage I (normoalbuminuria) - ACR < 30 mg/g.

DN stage II (microalbuminuria) – ACR 30- 300 mg/g.

DN stage III (macroalbuminuria) - ACR >300 mg/g and eGFR >30 mL/min/1.73m2.

DN stage IV: ACR > 300 mg/g and eGFR <30 mL/min/1.73m2.

Inclusion Criteria

1. Patients of both sex aged between 18 to 80 years
2. All patients with type 2 diabetes mellitus

Exclusion Criteria

1. Patients with age less than 18 and more than 80
2. Excessive alcohol ingestion(Consumption >21 drinks on average per week, 1 alcoholic drink =10 grams of alcohol)
3. Wilson disease
4. Lipodystrophy
5. Starvation
6. Parenteral nutrition
7. Medications like amiodarone, methotrexate, tamoxifen, corticosteroids valproate, anti-retroviral, antitubercular medicines.
8. History of viral hepatitis, obesity related surgery
9. Patients in congestive cardiac failure (CCF).

SAMPLE SIZE ESTIMATION

$$\text{Sample Size} = \frac{Z^2_{1-\alpha/2} * p * (100-p)}{d^2}$$

P	Percentage of NAFLD in India	49%
1-α	Confidence level	0.95
Z	Z value associated with confidence	1.96
D	Absolute precision (Value less than P)	10%

$$\text{Sample Size} = \frac{1.96^2 * 49 * (100-49)}{10^2}$$

Sample size 96 rounded up to 100.

Data Analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

Table[1]shows the percentage of diabetic population having NAFLD.

According to our study the prevalence of nonalcoholic fatty liver disease in type 2 diabetes mellitus is 40%.

Mean FBS Comparison with Respect To NAFLD

Mean FBS in NAFLD Positive was 112.15 ± 32.99and in NAFLD Negative was 122.3 ± 34.66. There was no significant difference in mean FBS comparison between two groups.

Mean PPBS comparison with respect to NAFLD

Mean PPBS in NAFLD Positive was 160.38 ± 32.91and in NAFLD Negative was 168.62 ± 32.32. There was no significant difference in mean PPBS comparison between two groups.

Mean TGL Comparison with Respect to NAFLD

Mean TGL in NAFLD Positive was 182.98 ± 40.97 and in NAFLD Negative was 157.05± 27.567. There was Significant difference in mean TGL comparison between two groups. (P Value = < .001)
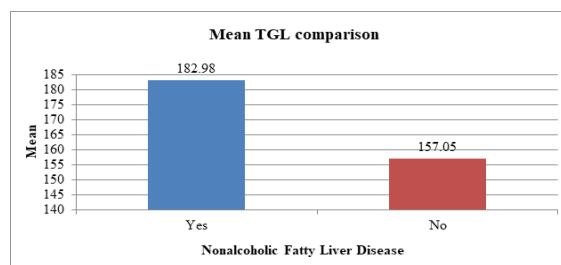

Figure 1: Bar Diagram Showing Mean TGL comparison with respect to NAFLD

Mean Total Cholesterol Comparison with Respect to NAFLD

Mean Total cholesterol in NAFLD Positive was 238.63 ± 31.18 and in NAFLD Negative was 232.60

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± 32.94. There was significant difference in mean Total cholesterol comparison between two groups. (P Value = 0.028).
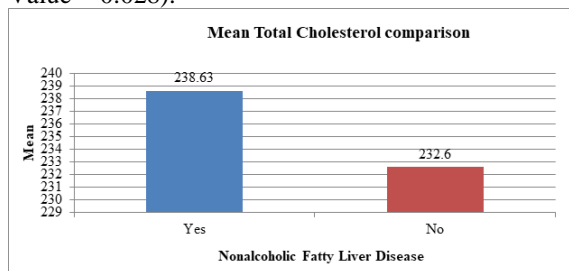

Figure 2: Bar Diagram Showing Mean Total cholesterol comparison with respect to NAFLD

Mean Total Protein Comparison with Respect to NAFLD

Mean Total protein in NAFLD Positive was 7.03 ± 0.39and in NAFLD Negative was 7 ± 0.45. There was no significant difference in mean Total protein comparison between two groups.

Mean albumin comparison with respect to NAFLD

Mean Albumin in NAFLD Positive was 3.93 ± 0.41and in NAFLD Negative was 3.99 ± 0.47. There was no significant difference in mean Albumin comparison between two groups.

Mean AST comparison with respect to NAFLD

Mean AST in NAFLD Positive was 43.25 ± 23.73and in NAFLD Negative was 37.5 ± 6.16. There was no significant difference in mean AST comparison between two groups.

Mean ALT comparison with respect to NAFLD

Mean ALT in NAFLD Positive was 48.3 ± 38.18and in NAFLD Negative was 38.12 ± 5.1. There was a significant difference in mean ALT comparison between two groups.
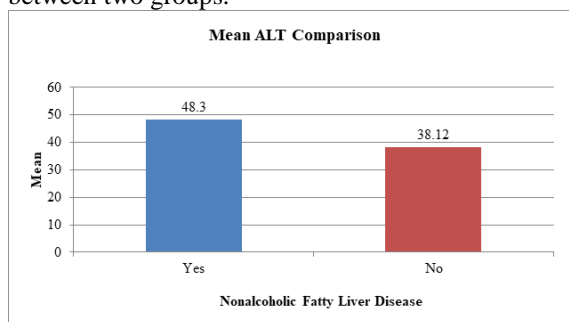

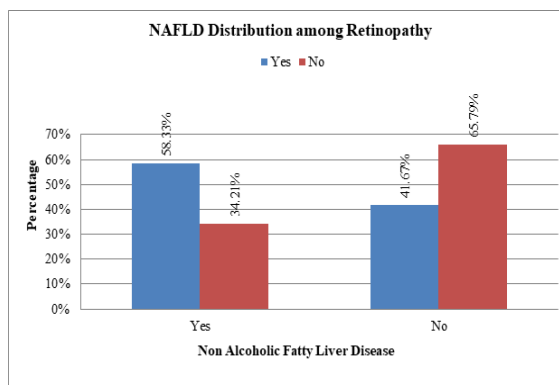**Figure 3: Bar Diagram Showing Mean ALT comparison with respect to NAFLD**

Figure 4: Bar Diagram Showing NAFLD Distribution among Retinopathy.

NAFLD Distribution Among Retinopathy

Out of 100 patients with diabetes 24 patients had retinopathy. Out of 40 patients with NAFLD 14 had retinopathy and 26 did not have retinopathy. So prevalence of retinopathy is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group (14 vs 10) which is statistically significant. (p value = 0.035).

NAFLD distribution among peripheral neuropathy

Out of 100 patients with diabetes 18 patients had peripheral neuropathy. Out of 40 patients with NAFLD, 14 had peripheral neuropathy and 26 did not have peripheral neuropathy. The prevalence of peripheral neuropathy among no NAFLD group is 4. So in our study the prevalence of peripheral neuropathy is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group (14 vs 4). That is subjects with NAFLD had higher risk for Retinopathy compared to those without NAFLD which is statistically significant (p value = < 0.001).
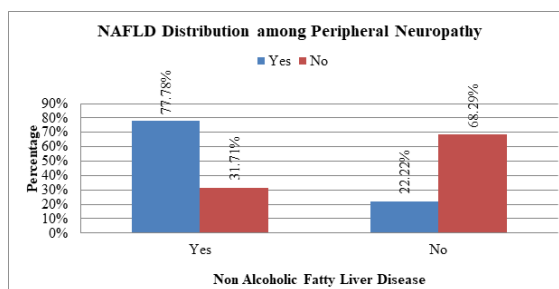

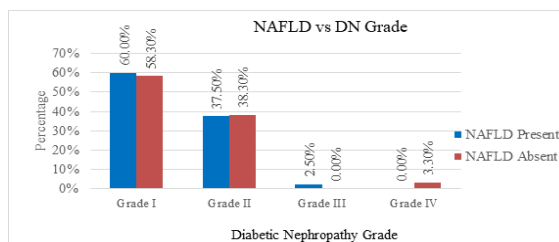**Figure 5: Bar Diagram Showing NAFLD Distribution among Peripheral Neuropathy**

Figure 6: Bar diagram showing Diabetic Nephropathy grade with respect to Non-alcoholic Fatty Liver Disease
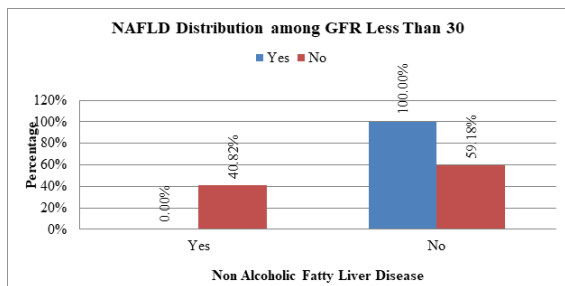
Figure 7: Bar Diagram Showing NAFLD Distribution among GFR Less Than 30

Diabetic nephropathy grade with respect to nonalcoholic fatty liver disease

Out of 100 patients with diabetes 59 patients are in grade 1 diabetic nephropathy, 38 patients are in grade 2 diabetic nephropathy, 1 patient is in grade 3 diabetic nephropathy,2 patient is grade 4 diabetic nephropathy. Out of 40 diabetic patients with NAFLD 24 patients are in grade 1 diabetic nephropathy, 15 patients are in grade 2diabetic nephropathy and 1 patient in grade 3 and 0 patient in grade 4 nephropathy. There was no significant association between DN and NAFLD.

NAFLD distribution among GFR less than 30

Out of 100 patients with diabetes only 2 had GFR less than 30. In our study no patients with NAFLD and diabetes had GFR less than 30 and it is statistically insignificant (p value = 0.243).

Table 1:Prevalance

Diabetic patients	Frequency	Percent
NAFLD	40	40%
No NAFLD	60	60%
Total	100	100%

Table 2: Shows the Mean FBS comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
FBS	112.15	32.99	122.3	34.66	0.147

Table 3: Shows the Mean PPBS comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
PPBS	160.38	32.91	168.62	32.32	0.218

Table 4: Shows the Mean TGL comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
TGL	182.98	40.972	157.05	27.567	< .001

Table 5: Shows the Mean Total cholesterol comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
Total Cholesterol	238.63	31.181	232.60	32.941	0.028

Table 6: Shows the Mean Total protein comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
Total Protein	7.03	0.39	7	0.45	0.687

Table 7: Shows the Mean Albumin comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
Albumin	3.93	0.41	3.99	0.47	0.507

Table 8: Shows the Mean AST comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
AST	43.25	23.73	37.5	6.16	0.076

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Table 9: Shows the Mean ALT comparison with respect to NAFLD

	Nonalcoholic Fatty Liver Disease				P Value
	Yes		No		
	Mean	Sd	Mean	Sd	
Alt	48.3	38.18	38.12	5.1	0.044*

Table 10: Shows the NAFLD Distribution among Retinopathy

		Retinopathy				Odds Ratio	95% Confidence Interval
		Yes		No			
		Count	%	Count	%		
Nonalcoholic Fatty Liver Disease	Yes	14	58.33%	26	34.21%	2.692	1.052, 6.89
	No	10	41.67%	50	65.79%		

$\chi2 = 4.423$, df = 1, p = 0.035*

Table 11: Shows the NAFLD Distribution among Peripheral Neuropathy

		Peripheral Neuropathy				Odds Ratio	95% Confidence Interval
		Yes		No			
		Count	%	Count	%		
Nonalcoholic Fatty Liver Disease	Yes	14	77.78%	26	31.71%	7.538	2.26, 25.14
	No	4	22.22%	56	68.29%		

$\chi2 = 13.053$, df = 1, p = < 0.001*

Table 12: Shows the Diabetic Nephropathy grade with respect to Nonalcoholic Fatty Liver Disease

		Nonalcoholic Fatty Liver Disease					
		Yes		No		Total	
		Count	%	Count	%	Count	%
DN grading	Grade I	24	60.0%	35	58.3%	59	59.0%
	Grade II	15	37.5%	23	38.3%	38	38.0%
	Grade III	1	2.5%	0	0.0%	1	1.0%
	Grade IV	0	0.0%	2	3.3%	2	2.0%
	Total	40	100.0%	60	100.0%	100	100.0%

$\chi2 = 2.849$, df = 3, p = 0.415

Table 13: Shows the NAFLD Distribution among GFR Less Than 30

		GFR Less Than 30 or Nephropathy			
		Yes		No	
		Count	%	Count	%
Nonalcoholic Fatty Liver Disease	Yes	0	0.00%	40	40.82%
	No	2	100.00%	58	59.18%

$\chi2 = 1.361$, df = 1, p = 0.243

DISCUSSION

Nowadays the prevalence of nonalcoholic liver disease is raising in the general population especially those with diabetes, metabolic syndrome, and obese individual. There is geographic variation in the prevalence of nonalcoholic liver disease.

Prevalence: The prevalence of nonalcoholic liver disease in the type 2 diabetic population in SSIMS AND RC medical college is 40% .Based on one study in type 2 diabetes mellitus that was conducted in north India using liver histology in the diagnosis of non-alcoholic liver disease, the prevalence of NAFLD was 88%,the prevalence of NASH was 63% and the prevalence of fibrosis was 38%.[1] In our study the prevalence of nonalcoholic liver disease was made using imaging modality as per definition of The American Association for the study of Liver Diseases (AASLD). According to Schwenzer et al ultrasound had a sensitivity and specificity of up to 94% and upto 95% respectively in making the diagnosis of nonalcoholic liver disease.[2] According to Bellentani et al the prevalence of non-alcoholic liver disease among type 2 diabetes mellitus was 30 to 50%.[3]

Blood glucose levels: According to our study there is no significant difference in mean FBS and PPBS comparison between two groups. The mean fasting blood glucose level of NAFLD group and no NAFLD group was 112.15 vs 122.3 mean postprandial blood glucose level of NAFLD group and no NAFLD group was 160.38 vs 168.62.

According to Jimba et al the prevalence of NAFLD is high among the individuals having high blood sugar in general population.[4] According to S.Bajaj et al the diabetic patients with NAFLD had high fasting blood sugar levels and insulin levels.[5]

Dyslipidemia: According to our study the diabetic NAFLD patient had high total cholesterol and high triglycerides level than compared with no NAFLD patients which are statistically significant. The mean TGL and Total cholesterol were 182.98 vs 157.05, and 238.63 vs 233.37 in NAFLD and no NAFLD patients. So dyslipidaemic individuals are at high risk of getting NAFLD.

According to Chatrath H et al NAFLD individuals often had altered lipid metabolism along with the

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characteristics of metabolic syndrome. The NAFLD individual usually will have increased triglycerides, increased LDL (nontype A) particles and decreased HDL. The altered lipid metabolism in NAFLD is due to overproduction VLDL by the liver and decreased clearance of lipid by the liver.[6]

Serum albumin level: In our study the mean albumin in NAFLD and no NAFLD group was 3.93 vs 3.99. Even though the NAFLD patients had low albumin than no NAFLD group, there was no statistical significance. According to Younossi ZM et al low albumin, high bilirubin, and increased prothrombin time are the predictor's of mortality in NAFLD patients.[7] According to Fierbinteanu-Braticevici et al CRP, splenic longitudinal diameter, insulin resistance scale, body mass index, albumin, GGT, INR, age are correlated well with NASH. The four predictors of NASH are - CRP (p=0.004), SLD (p=0.018), HOMA (p=0.03) and albumin level (p=0.041), the albumin (p=0.008), is associated with severe fibrosis.[8]

Transaminases levels: In our study elevation of ALT is statistically significant in NAFLD patients when compared with that of no NAFLD patients. There is no correlation between NAFLD and AST levels.

A study was conducted by Ioannou et al based on 10-year risk of cardiovascular events by Framingham risk score (FRS) in individuals with normal and elevated ALT levels. The ALT is said to be elevated when it is more than 43 IU/L. According to this study the elevated ALT are associated with high FRS score.[9]

According to a Swedish study mortality in patients with NAFLD increased with elevated liver enzyme level. ALT level varies according to the severity of liver steatosis than GGT levels. According to Kotronen A et al ALT rise correlate with increased cardiovascular mortality.[10]

Diabetic Nephropathy: According to our study there is no correlation between albuminuria and NAFLD in the diabetic patients. The no NAFLD group had severe forms of diabetic nephropathy namely stage 4 nephropathy.

According to the study conducted by Yucihiro et al a study which was conducted in japan there is no relationship between NAFLD and diabetic nephropathy among diabetic population.[11] A large study conducted in south India by Vishwanathan et al found that NAFLD and diabetic nephropathy among diabetic population had no correlation.[12] According to the study conducted by Hwang ST et al there is very good relationship between NAFLD and microalbuminuria and newly detected diabetes and with prediabetes.[13]

Diabetic Neuropathy: According to our study there is a very strong correlation between NAFLD diabetic patients and peripheral neuropathy. According to Yuichiro Takeuchi et al there is no correlation between NAFLD and neuropathy.[11] According to Vishwanathan et al who conducted study in south India NAFLD and neuropathy are strongly

correlated.[12] According to study conducted by Lv WS et al negatively correlated diabetic retinopathy and diabetic neuropathy with NAFLD patients.[14]

Diabetic Retinopathy: According to our study there is a strong correlation between NAFLD and diabetic retinopathy. According to LvWS et al NAFLD and diabetic retinopathy are negatively correlated.[14] According to Yuichiro Takeuchi et al there is no correlation between NAFLD and retinopathy.[11] According to Vishwanathan et al who conducted study in south India NAFLD and retinopathy are strongly correlated.[12] According to study conducted in type 2 diabetes mellitus by Targher G, Bertolini L et al the prevalence of chronic kidney disease and diabetic retinopathy is high among NAFLD individuals.[15]

Limitations of the study

1. Our study has been done among the population attending SSIMS and RC hospital OPD and there can be a bias in selecting such a group of population, so this study has to be done among the general population or it has been done at multiple centers and meta-analysis of those studies can provide a significant conclusion of this issue.

2. Sample size was small so further studies with bigger sample size has to be done to further verify the results.

CONCLUSION

➢ In my study the diabetic patients with NAFLD have high triglyceride and high total cholesterol level

➢ In my study the diabetic patients with NAFLD had high prevalence of diabetic retinopathy.

➢ In my study the diabetic patients with NAFLD had high prevalence of diabetic peripheral neuropathy.

➢ In my study the diabetic patients with NAFLD did not have any relation with diabetic nephropathy.

Thus NAFLD in type 2 diabetes mellitus is an independent predictor of diabetic microangiopathy.

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