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Correlation Of Non Alcoholic Fatty Liver Disease And Glycemic Control In Patients With Type 2 Diabetes Mellitus

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ABSTRACT:
Background*: Non Alcoholic Fatty Liver Disease (NAFLD) is now the most common cause of chronic liver disease in the developed world, with 25% prevalence globally, and is rising in incidence due to the obesity pandemic. NAFLD and T2DM share common pathogenic mechanisms and both coexist in many individuals. Previous studies established its relation with metabolic syndrome and its components including T2DM. Inspite of being a global pandemic, the screening tools for NAFLD are still lacking. This study was aimed at establishing a positive correlation of NAFLD in T2DM patients with markers of glycemic control, so as to use them as screening tools for early identification and treatment initiation among high risk groups.*
Objectives*:*
1. *To assess the correlation between NAFLD and glycemic control in patients with Type 2 Diabetes Mellitus.*
2. *To assess the correlation between NAFLD and BMI in the patients studied.*

Methodology*: A total of 45 patients fulfilling the inclusion criteria and exclusion criteria, attending the OPD and admitted to Government Medical College, Kottayam were selected for the study. After obtaining written informed consent, a detailed history, anthropometric measurements (BMI), clinical examination and laboratory tests including LFT, HbA1C (Using immunoassay method), FBG, FLP, Hepatitis B or C virus as well as S. Ceruloplasmin, S. Ferritin, PT/INR and APTT and USG of the liver were performed, and semi-structured proforma was filled up. Patients were divided into groups based on their HbA1C as A1: ≤7 and A2: HbA1c >7 and based on BMI as B1 : <18.5, B2 : 18.5- 22.9, B3 : 23- 24.9, B4 : 25- 30. The collected data was then analysed using SPSS software to assess if there was any correlation between NAFLD and HbA1C levels.*

Results*: Out of the 45 patients studied, 77.8% (35) patients had sonologically normal liver, 11% patients (5) had grade 1 fatty liver, 6.7% (3) had grade 2 fatty liver and 4.4% (2) patients had cirrhosis. 43 out of 45 patients had HbA1C more than or equal to 7 and 2 patients had HbA1C less than 7. A positive but statistically insignificant association was established between HbA1c levels and NAFLD prevalence (p value of 0.43). The mean BMI in patients with NAFLD (25 kg/m^2) was found to be higher than that of the non-NAFLD group which was 21.8 kg/m^2 but had no statistical significance. A statistically significant correlation between years lived with diabetes and incidence of NAFLD was found with a p value of 0.031.*

Conclusion: *According to the study, duration of diabetes mellitus is a better predictor of NAFLD than glycemic control and BMI.*

Keywords*: T2DM patients, NAFLD, screening, glycemic control, BMI, duration of T2DM*

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I. Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) is now the most common cause of chronic liver disease in the developed world. The prevalence of NAFLD is 25% and is increasing because of the global obesity epidemic[1]. There is a complex causative – consequence or bidirectional relationship between metabolic syndrome and NAFLD[2]. The prevalence also increases with age and older age groups have high mortality rates.

NAFLD comprises of a spectrum of diseases ranging from simple steatosis to steatohepatitis to cirrhosis which may then progress to hepatocellular carcinoma[3]. There is a high prevalence of NAFLD in patients already diagnosed with T2DM[4] and previous studies estimated that 56% and 37% of patients with T2DM are affected by NAFLD and NASH respectively[5]. Reduced intestinal barrier function in obese individuals stimulate production of inflammatory cytokines by the hepatocytes due to increased exposure to gut derived substances[6]. These cause insulin resistance and eventually result in hyperglycemia. Moreover, cytokines released by adipocytes[7], epigenetic factors[8], and inflammasomes also play significant roles[9]. Therefore, NAFLD and diabetes coexist in many

individuals. Imaging modalities like USG, CT and MRI can be used to detect the presence of fat in the liver. Transient Elastography or Fibro Scan is an ultrasound based imaging technique that can be used to detect the degree of liver fibrosis[10].

Blood glucose levels form glycosylated hemoglobin (HbA_{1C}) non-enzymatically as an irreversible reaction. Once formed, HbA_{1C} remains in blood circulation for 2-3 months. Since HbA1c is a reliable indicator of Diabetic control[11], it may be assumed that, higher HbA1c levels would be associated with higher incidence of NAFLD. In a study conducted by Bendwal S et al., a statistically significant correlation was found between NAFLD and high HbA1c levels, with 56.31% of patients with NAFLD having HbA1c level of more than 7%[12].

No single intervention has been proven to be curative for NAFLD. Lifestyle modifications and pharmacological therapies are used in combination to treat the risk factors as well as to prevent progression and if possible, to revert the condition[5].

II. Materials and Methods

Study design: Cross sectional observational study which was approved by the Institutional Review Board and Institutional Ethics Committee

Study Population : Patients with Type 2 Diabetes Mellitus attending the OPD and admitted under the Department of General medicine, Government Medical College, Kottayam

Inclusion Criteria
All the patients of T2DM above the age of 18 years and satisfying the ADA 2021 guidelines.

Exclusion Criteria

- Patients taking any medications that are known to alter liver functions which include antiepileptics, amiodarone, antituberculous drugs, azathioprine, methotrexate, risperidone, quetiapine except antidiabetic drugs and statins.
- Patients with hypothyroidism.
- Patients admitted with Acute or Chronic Liver disease.
- Patients with history of Hepatitis B or C.
- Patients with Chronic Kidney Disease
- Patients taking alcohol more than 20 g/day for women and more than 40 g/day for men.

Methodology: A total of 45 patients fulfilling the inclusion criteria and exclusion criteria, attending the OPD and admitted to Government Medical College, Kottayam were selected for the study. After obtaining written informed consent, a detailed history, anthropometric measurements (BMI), clinical examination and laboratory tests including LFT, HbA1C (Using immunoassay method), FBG, FLP, Hepatitis B or C virus as well as S. Ceruloplasmin, S. Ferritin, PT/INR and APTT and USG of the liver were performed, and semi-structured proforma was filled up. Patients were divided into groups based on their HbA1C as A1: ≤7 and A2 : HbA1c >7 and based on BMI as B1 : <18.5, B2 : 18.5- 22.9, B3 : 23- 24.9, B4 : 25- 30. Abdominal ultrasound report of Grade 1, Grade 2 or Grade 3 fatty liver as well as Liver Cirrhosis were considered as Non Alcoholic Liver disease in the absence of any other risk factors.

Sample Size: From a previous 2017 study titled "The Relationship Between Glycaemic Control and Non-Alcoholic Fatty Liver Disease in Nigerian Type 2 Diabetic Patients" done by Babalola Ishmael Afolabi et al. in Obafemi Awolowo University (OAU)/OAU Teaching Hospitals Complex, Ile Ife, Nigeria, the prevalence of NAFLD in patients with Type 2 diabetes mellitus was found to be 69%[13].

$N = \frac{4pq}{d^2} = \frac{4\times69\times31}{13.8\times13.8} = 44.93 = 45$

NB: N = sample size, p = prevalence = 69, q =100-p = 31, d = absolute error = 20% of p = 13.8
Total sample size = 45

Statistical Analysis: Data was entered in Microsoft Excel and analysed using IBM SPSS Statistics for windows, Version 20.0 Armonk, NY: IBM Corp.

III. Confidentiality

Strict confidentiality was ensured by keeping the identity of the patients anonymous and the information obtained used only for the scientific publication.

IV. Ethical Considerations

The proposal of the study was presented before the Institutional Review Board and the study was approved by the Institutional Ethics Committee. Written informed consent was taken from all the study subjects.

V. Analysis Of Data

Data was entered in Microsoft Excel and analyzed using IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp. IBM Corp.. Categorical variables used were expressed as frequency (percentage) and continuous variables were expressed in mean and standard deviation. Comparison of mean age, BMI, Years living with Diabetes mellitus and HbA1C between the various USG diagnosis finding were done using One-Way-ANOVA and post-hoc was done using Tukey's test. Association of categorical variables like Gender, BMI group, Hypertension, Dyslipidemia, Alcohol Use, Frequency of Alcohol Consumption, Years with Diabetes group and HbA1C groups were done using Pearson Chi-square test. For all these statistical interpretations, $p< 0.05$ was considered the threshold for statistical significance.

VI. Results

TABLE 6.1: Description Of The Population I

Parameters	N	Mean	Std. Deviation
Age	45	58.49	13.21
BMI	45	22.42	2.91
Age of DM diagnosis	45	48.98	12.23
Years living with diabetes	45	9.47	7.70
HbA1C	45	9.24	1.44

Table 6.2: Description Of The Population Ii

Variables	Levels	Frequency	Percent
Gender	Male	27	60.0
	Female	18	40.0
Dyslipidemia	Absent	21	46.7
	Present	24	53.3
Hypertension	Absent	23	51.1
	Present	22	48.9
Alcohol use	Absent	32	71.1
	Present	13	28.9
If present, Frequency of alcohol use	Once in 2-3 weeks	1	7.7
	Once in a month	2	15.4
	Occasional	10	76.9
USG Abdomen	Normal	35	77.8
	Grade 1 fatty liver	5	11.1
	Grade 2 fatty liver	3	6.7
	Liver cirrhosis	2	4.4
Years with DM	≤ 10 years	31	68.9
	>10 years	14	31.1
HbA1C status	≤ 7%	2	4.4
	>7%	43	95.6
BMI group (kg/m^2)	<18.5	2	4.4
	18.5 – 22.9	23	51.1
	23 – 24.9	11	24.4
	25 – 29.9	9	20.0

Inference

There is no statistically significant difference in the mean age or BMI across the patients with different USG abdomen outcomes.

Inference

There is no statistically significant difference in the mean age of DM diagnosis and HbA1C across the patients with different USG abdomen outcomes.

Table 6.3: Comparison Of Mean Age And BMI Across The USG Abdomen Outcomes

Patient characteristics	USG Abdomen	No.	Mean	Std. Deviation	Std. Error	F	P value
Age	Normal	35	57.46	13.4	2.27	0.74	0.54
	Grade 1 fatty liver	5	66.60	16.5	7.38		
	Grade 2 fatty liver	3	59.33	5.5	3.18		
	Liver cirrhosis	2	55.00	0.0	0.0		
BMI	Normal	35	21.99	2.63	0.45	1.43	0.247
	Grade 1 fatty liver	5	23.46	3.05	1.36		
	Grade 2 fatty liver	3	23.67	5.50	3.18		
	Liver cirrhosis	2	25.50	2.12	1.50		

**P value <0.05 is considered statistically significant*
One-Way ANOVA test

Table 6.4: Comparison of mean diabetic characteristics across the USG outcomes

Diabetes characteristics	USG Abdomen	N	Mean	Std. Deviation	Std. Error	F	P value
Age of DM diagnosis	Normal	35	49.14	11.31	1.91	1.58	0.21
	Grade 1 fatty liver	5	53.20	18.62	8.33		
	Grade 2 fatty liver	3	51.33	9.07	5.24		
	Liver cirrhosis	2	32.00	0.0	0.0		
Years living with diabetes	Normal	35	8.31	6.69	1.13	3.27	0.031*
	Grade 1 fatty liver	5	13.40	11.90	5.32		
	Grade 2 fatty liver	3	7.33	2.89	1.67		
	Liver cirrhosis	2	23.00	0.0	0.0		
HbA1C	Normal	35	9.07	1.38	0.23	0.94	0.43
	Grade 1 fatty liver	5	9.57	1.57	0.70		
	Grade 2 fatty liver	3	9.87	2.27	1.31		
	Liver cirrhosis	2	10.51	0.42	0.30		

**P value <0.05 is considered statistically significant*
One-Way ANOVA test

Table 6.5: Post Hoc comparison for years living with diabetes using Dunn's Test

Table 6.5: Post Hoc comparison for years living with diabetes using Dunn's Test

(I) USG Abdomen	(J) USG Abdomen	Mean Difference (I-J)	P value
Normal	Grade 1 fatty liver	-5.09	0.456
Normal	Grade 2 fatty liver	0.98	0.996
Normal	Liver cirrhosis	-14.69	0.036*
Grade 1 fatty liver	Grade 2 fatty liver	6.067	0.656
Grade 1 fatty liver	Liver cirrhosis	-9.60	0.390
Grade 2 fatty liver	Liver cirrhosis	-15.67	0.094

**P value <0.05 is considered statistically significant*

Table 6.6: Association of gender and BMI with USG abdomen results

Patient characteristic.	Levels	USG Abdomen				$\chi 2$	P value
		Normal n (%)	Grade 1 fatty liver n (%)	Grade 2 fatty liver n (%)	Liver cirrhosis n (%)		
Gender	**Male**	19 (70.4)	4 (14.8)	2 (7.4)	2 (7.4)	2.69	0.44
	Female	16 (88.9)	1 (5.6)	1 (5.6)	0 (0.0)		
BMI group (Kg/m^2)	**< 18.5**	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5.99	0.74
	18.5 – 22.9	19 (82.6)	2 (8.7)	2 (8.7)	0 (0.0)		
	23 – 24.9	9 (81.8)	1 (9.1)	0 (0.0)	1 (9.1)		
	25 – 29.9	5 (55.6)	2 (22.2)	1 (11.1)	1 (11.1)		

P value <0.05 is considered statistically significant.
Pearson Chi-Square test.

Inference
There is no statistically significant association between BMI and Liver charecteristics on USG Abdomen.

Table 6.9: Association of diabetes variables with USG abdomen results

Characteristic	Levels	USG Abdomen				$\chi 2$	P value
		Normal n (%)	Grade 1 fatty liver n (%)	Grade 2 fatty liver n (%)	Liver cirrhosis n (%)		
Years with DM	**≤ 10 years**	26 (83.9)	2 (6.5)	3 (9.7)	0 (0.0)	8.21	0.046*
	> 10 years	9 (64.3)	3 (21.4)	0 (0.0)	2 (14.3)		
HbA 1C	**< 7%**	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.29	0.96
	≥ 7 %	34 (77.3)	5 (11.4)	3 (6.8)	2 (4.5)		

P value <0.05 is considered statistically significant.
Pearson Chi-Square test.

Inference
There is a statistically significant association between years with DM and the USG results. Those who had liver cirrhosis had DM for more than 10 years.
There is no statistically significant association between HbA1C status and the USG results.

VII. Discussion

In the study population of 45 patients, 27 (60%) were males and 18 (40%) were females. The mean age of the study population was 58.49 years.

Among the 45 patients, 35 had sonologically normal liver, 5 had Grade 1 fatty liver,3 had Grade 2 fatty liver and 2 had Cirrhosis.

Though there was a positive association between HbA1c levels and sonologically evident liver disease as the mean HbA1c in the NAFLD group was 9.84 % and that of the Non-NAFLD group was 9.07 %, this correlation was not found to be significant statistically with a p value of 0.43. Similarly the mean BMI in patients with NAFLD (25 kg/m2) was found to be higher than that of the Non-NAFLD group which was 21.8 kg/m2 which was also not found to have any statistical significance.

However there was statistically significant correlation between years lived with Diabetes and incidence of fatty liver disease as found using One-Way-ANOVA test with a p value of 0.031.

Post Hoc comparison using Dunn's Test revealed that the years of living with DM is significantly higher for patients who have sonologically evident Chronic parenchymal liver disease than those are normal.

A statistically significant association between the habit of alcohol consumption and presence of NAFLD was found (p value-0.046). The safety limit of alcohol consumption to rule-in NAFLD might be lower in the population represented by the study sample.

VIII. Conclusions

According to the study, HbA1c is not a good predictor of NAFLD in diabetic patients
According to the study, BMI is also not a good predictor of NAFLD
Duration of Diabetes Mellitus seems to be better predictor of NAFLD than other variables studied (HbA1c, BMI).

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