Association Of Microvascular And Macrovascular Complications With Non Alcoholic Fatty Liver Disease(Nafld) In Type 2 Diabetes Mellitus- A Comparative Cross Sectional Study.

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Abstract
NAFLD in patients with type 2 diabetes mellitus play an important role in development of micro and macrovascular complications. NAFLD results in Type 2 Diabetes Mellitus by increasing insulin resistance(6) and pancreatic β-cell lipotoxicity caused by sustained elevation in FFAs formed from lipolysis of adipose tissue resulting in defective insulin secretion. NAFLD is found to be independently associated with an increased prevalence of Diabetic complications. Our study aims to look for an association between NAFLD and micro vascular and macro vascular complications of Type2DM. This comparative cross sectional study was conducted in the patients who attended the OPD in the Department of Diabtology from June – Oct 2017. A total of 60 patients were included in the study. The Urine PCR for Diabetic Nephropathy and Fundus changes for Diabetic Retinopathy were found to be significantly (p<0.05) increased the patients with NAFLD. Hence forth the above study showed as association between NAFLD and the development of micro and macro vascular complications in Type 2 Diabetes Mellitus patients.

I   Introduction

According to the World Gastroenterology Organization's global guidelines, the overall prevalence of NAFLD varies from 4% to 46% across the world(1).Various studies conducted in Indian population, showed that the prevalence rate of NAFLD was around 9-32% and with a higher incidence of NAFLD among Type 2 Diabetes Mellitus(T2DM) individuals ranging from 12.5% to 87.5%(2).

The term NAFLD includes a wide array of fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma, in the absence of excessive alcohol intake(4).

Only recently, NAFLD has been increasingly recognized as the liver disease component of metabolic syndrome(3).

Various studies have shown that T2DM patients appear to have an increased risk of developing NAFLD than nondiabetic subjects and certainly have higher risk of developing fibrosis and cirrhosis[4].

Current preclinical data suggest that selective hepatic sensitivity to insulin and hyperinsulinemia leads to increased adipose tissue lipolysis and increased free fatty acid(FFAs) delivery to the liver, enhancing stimulation of hepatic lipid synthesis. Moreover, increased cellular oxidant stress leading to fibrosis by activation of Hepatic Stellate Cells(5) has been implicated as the key for progression of NAFLD.

Zhang et al, approaching the relationship between NAFLD and diabetes from another perspective, have proven that hepatic steatosis precedes the development of T2DM(13).

The primary mechanism by which NAFLD contributes to T2DM is by increasing insulin resistance(6) and pancreatic β-cell lipotoxicity caused by sustained elevation in FFAs formed from lipolysis of adipose tissue resulting in defective insulin secretion(8).

Previous studies done by Targher et al(9,10) and Casoinic et al(11) showed that NAFLD was independently associated with an increased prevalence of proliferative diabetic retinopathy and cardiovascular risk, and diabetic nephropathy in T2DM, respectively.

Ultrasonography of abdomen seems to be a non-invasive, cost effective, simple procedure to detect the fatty changes in liver(12). Hence, considering the concept of bidirectional relationship between NAFLD and T2DM, assessing the hepatic status for fatty infiltration could be an ideal marker of insulin resistance in T2DM and its complications early(7).

Therefore the aim of the study is to find a correlation between NAFLD detected by Ultrasonography and micro-vascular and macro-vascular complications in T2DM.

II   Materials And Methods

- STUDY DESIGN: Comparative Cross-sectional study.
- STUDY CENTRE: Department of Diabetology, Department of Radiology, Department of Ophthalmology and Department of Biochemisty in our institution.
- STUDY PERIOD: June – Oct 2017.
- STUDY POPULATION: Total sample size 60 T2DM patients(30 with NAFLD and 30 without NAFLD)

CALCULATION OF SAMPLE SIZE:

The sample size was calculated with Two sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
% patients without NAFLD with Outcome:	7.8
% patients with NAFLD with Outcome:	38
Odds Ratio:	7.2
Risk/Prevalence Ratio:	4.9
Risk/Prevalence difference:	30

Total sample size = 60 (30 with NAFLD and 30 without NAFLD).
Inclusion criteria:
CASES: Diagnosed Type 2 DM Patients between 5 to 15 years duration of diabetes with NAFLD confirmed by Ultrasonography and without any other comorbidities.
Exclusion criteria:
Diabetic patients with obvious liver disease due to other causes (Hepatitis B, C), patients with a history of exposure to hepatotoxic agents like alcohol and others medications were excluded from the study.
CONTROLS: Type 2 DM Patients between 5 to 15 years duration of diabetes without NALFD confirmed by Ultrasound of liver.

Subjects and selection methods:
This Comparative Cross-sectional study was conducted in the patients who attended the Department of Diabetology with 30 individuals in each group with age, sex and duration of diabetes matched, in an attempt to find an association between NAFLD and Micro and Macrovascular complications in Type 2 Diabetes Mellitus.
Procedure methodology:
ROUTINE INVESTIGATIONS:
Under strict aseptic conditions 5ml of blood sample is collected by venipuncture, into labeled plain polystyrene tubes. Blood samples are centrifuged at 5000 rpm for10 min and the serum is stored at -20◦ C until further analysis.
FASTING PLASMA GLUCOSE:
METHOD: GOD/POD method (enzymatic, end point analysis)
PRINCIPLE: Glucose present in the plasma is oxidized by the enzyme glucose oxidase (GOD) to gluconic acid with the liberation of hydrogen peroxide, which is converted to water and oxygen by the enzyme peroxidase (POD). 4-aminophenazone, an oxygen acceptor, takes up the oxygen and together with phenol forms a pink coloured chromogen which can be measured at 515 nm.

CHIEF INVESTIGATIONS:
1)   Ultrasonography of liver(to divide the study population into two groups):
All the T2DM patients will undergoabdominal ultrasonography by a single experienced radiologist for evidence of fatty liver and its grading was done as per the standard criteria, thereby dividing the T2DM into two groups as patients with NAFLD and withoutNAFLD.
The standard criteria accepted by the American gastroenterology association, the severity of NAFLD is graded as,
Grade 1: Slight diffuse increase in the fine echoes. Liver appears bright as compared to the cortex of the kidney. Normal visualisation of diaphragm and intrahepatic vessel borders.
Grade 2:Moderate diffuse increase in the fine echoes.Slightly impaired visualisation of the intrahepatic vessels and diaphragm.

<u>Grade 3</u>:Marked increase in the fine echoes. Poor or no visualisation of intrahepatic vessel borders, diaphragm and the vessels.

2)   <u>Fundoscopic examination of eye(to find Diabetic Retinopathy):</u>

Procedure:

- **Pupil dilation**: -bymydriaticdrops(Tropicamide eye drops).
- **Ophthalmoscopy** - examination of the retina done by

(1) Slit Lamp Biomicroscope with a special magnifying lens that provides a narrow view of the retina,
 (2) Direct Ophthalmoscope.
Any abnormal finding due to Diabetic Retinopathy will be noted.

3)   <u>Measurement of Diabetic Neuropathy(Biosthesiometry) :</u>

- The Biothesiometry – subjective methodology to find the vibration perception by applying 25V level vibration to the dorsal aspect of the distal phalanx of the hallux and to the dorsal aspect of the fifth metatarsal head.
- A threshold of 25V will be taken as the cut off value in the diagnosis of Diabetic Neuropathy.

4)   <u>Measurement of urine Protein to Creatinine ratio(PCR):</u>

- Colorimetric Reflectance Spectrophotometry will be used to measure the protein to Creatinine ratio in the urine sample.
- The normal protein-to-creatinine ratio: Males is <0.11 mg /mg of Creatinine

Females is <0.16 mg/ mg of Creatinine

5)   <u>Measurement of Ankle-Brachial Index:(for Peripheral Vascular Disease)</u>

- A Doppler Ultrasound blood flow detector will be used to measure the ankle-brachial index (ABI).

$$ABI = \frac{P_{leg}}{P_{arm}}$$

Where P_{Leg} is the systolic blood pressure of dorsalis pedis or posterior tibial arteries and P_{Arm} is the brachial systolic blood pressure, measured in both upper and lower limbs.
ABI<0.9 –taken as significant for the presence of peripheral vascular disease.

6)   <u>Assessment of Coronary Artery Disease(CAD):</u>
Coronary artery disease- diagnosed based on a patient's electrocardiographic(ECG) changes typical of ischemia (the presence of Q/Qs pattern, significant ST segment depression, or deep T wave inversion) and be the previous hospital medical record of myocardial infarction, angina pectoris, coronary artery bypass surgery, percutaneous coronary angioplasty.

DATA COLLECTION PROCEDURES AND INSTRUMENTS USED:
Data collection will be done using standardized proforma by the principal investigator. All the biochemical analyses will be performed using automated (robonik - Autora) and semi-automated (MERCK) clinical chemistry analyzer.

QUALITY CONTROL:
All biochemical analyses will be done with adequate internal and external quality checks, and within run and between run CV's will be maintained.

CONFIDENTIALITY:
Informed consent will be obtained from all patients. Confidentiality and safety of the subjects will be taken care of.

STATISTICAL ANALYSIS:

- Coded data are entered in excel sheet.
- It was analysed with SPSS 20.0 package.
- The micro and macrovascular complications in both groups was expressed as mean with standard deviation.
- The correlation between NAFLD and micro and macro vascular complications was expressed in terms of correlation coefficient- Pearson/Spearman.
- The difference in micro and macrovascular complications between the two groups was expressed as mean with standard deviation.
- $p \leq 0.05$ was considered as statistically significant for two tailed test.

III   Results

This comparative cross sectional study was conducted in the Department of Diabetology , Department of Radiology and Department of Ophthalmology with 30 individuals in each group with age ,sex and duration of

diabetes matched, in an attempt to find an association between NAFLD and Micro and Macrovascular complications in Type 2 Diabetes Mellitus.

Descriptive Statistics(cases)

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	30	48	62	54.50	3.655
HEIGHT	30	140	174	156.50	8.593
WEIGHT	30	46	86	66.87	9.526
BMI	30	22.4323	38.0499	27.308449	3.5103967
SBP	30	80	156	113.87	18.019
DBP	30	50	110	79.73	11.151
HbA1c	30	5.4000	14.2000	8.423333	1.9688406
FBS	30	101	255	157.10	38.960
TC	30	141	240	185.50	27.629
TGL	30	74	452	159.97	80.306
HDL	30	38	64	49.60	7.228
LDL	30	26	162	106.73	36.678
VLDL	30	15	104	38.00	22.428
SB	30	.5	1.3	.677	.1478
SGOT	30	13	37	22.07	6.848
SGPT	30	10	65	22.10	12.030
SAP	30	55	195	95.93	35.763
TP	30	5.9	7.8	6.937	.4817
ALB	30	3.0000	5.2000	4.173333	.4585835
GLB	30	2.0000	3.9000	2.776667	.4132990
UREA	30	21	48	26.47	4.508
CREATININE	30	.5000	1.3000	.963333	.1691425
PCR	30	16.0000	225.3000	73.466667	40.5924686
BIO	30	10	35	17.50	8.881
ABI	30	.7600	1.4400	1.003167	.1854467

Descriptive Statistics(controls)

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	30	42	63	56.60	4.673
HEIGHT	30	142	170	154.70	7.857
WEIGHT	30	40	88	60.73	10.262
BMI	30	17.7778	33.3319	25.357270	3.7817487
SBP	30	90	158	117.67	15.105
DBP	30	68	112	83.80	9.803
HbA1C	30	6.2000	11.0000	7.533333	1.2852836
FBS	30	95	249	141.17	35.424
TC	30	140	263	178.63	27.594
TGL	30	64	240	112.47	41.589
HDL	30	31	64	48.63	8.680
LDL	30	19	165	104.47	28.669
VLDL	30	13.0	94.0	25.500	16.4065
SB	30	.5	1.2	.697	.1564
SGOT	30	5	40	20.03	6.846
SGPT	30	10	44	17.00	6.638
SAP	30	52	273	97.73	44.164
TP	30	5.0	7.7	6.863	.6333
ALB	30	2.9000	5.1000	4.086667	.5217565
GLB	30	2.0000	3.5000	2.800000	.3850660
UREA	30	22	30	25.47	1.776
CREATININE	30	.7000	1.2000	.893333	.1337350
PCR	30	15.0000	118.5000	49.010000	27.4938407
BIO	30	10	30	13.67	5.862
ABI	30	.8400	1.2700	1.040333	.1183357
Valid N (listwise)	30				

SEX (case)

		Frequency	Percent	Valid Percent	Cumulative Percent
	F	12	40.0	40.0	40.0
Sex	M	18	60.0	60.0	100.0
	Total	30	100.0	100.0	

USG LIVER(case)

Fatty liver grading		Frequency	Percent	Valid Percent	Cumulative Percent
USG LIVER	1	11	36.7	36.7	36.7
	2	11	36.7	36.7	73.3
	3	8	26.7	26.7	100.0
	Total	30	100.0	100.0	

PCR(case)

		Frequency	Percent	Valid Percent	Cumulative Percent
PCR#	0	11	36.7	36.7	36.7
	1	19	63.3	63.3	100.0
	Total	30	100.0	100.0	

0-   patients without proteinuria
1-   patients with proteinuria

BIO(case)

		Frequency	Percent	Valid Percent	Cumulative Percent
BIO#	0	19	63.3	63.3	63.3
	1	11	36.7	36.7	100.0
	Total	30	100.0	100.0	

0-   patients with normal vibration perception
1-   patients with loss of vibration perception

ABI(case)

		Frequency	Percent	Valid Percent	Cumulative Percent
ABI#	0	17	56.7	56.7	56.7
	1	13	43.3	43.3	100.0
	Total	30	100.0	100.0	

0-   patients without peripheral vascular disease
1-   patients with peripheral vascular disease.

FUNDUS(case)

		Frequency	Percent	Valid Percent	Cumulative Percent
FUNDUS	0	23	76.7	76.7	76.7
	1	7	23.3	23.3	100.0
	Total	30	100.0	100.0	

0-   patients without diabetic retinopathy
1-   patients with diabetic retinopathy

SEX(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
SEX	F	16	53.3	53.3	53.3
	M	14	46.7	46.7	100.0
	Total	30	100.0	100.0	

USG LIVER(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
USG LIVER	0	30	100.0	100.0	100.0

PCR(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
PCR#	0	20	66.7	66.7	66.7
	1	10	33.3	33.3	100.0
	Total	30	100.0	100.0	

0-   patients without proteinuria
1-   patients with proteinuria

BIO(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
BIO#	0	26	86.7	86.7	86.7
	1	4	13.3	13.3	100.0
	Total	30	100.0	100.0	

0-   patients with normal vibration perception
1-   patients with loss of vibration perception

ABI(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
ABI#	0	25	83.3	83.3	83.3
	1	5	16.7	16.7	100.0
	Total	30	100.0	100.0	

0-   patients without peripheral vascular disease
1-   patients with peripheral vascular disease.

FUNDUS(control)

		Frequency	Percent	Valid Percent	Cumulative Percent
FUNDUS	0	29	96.7	96.7	96.7
	1	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

0-   patients without diabetic retinopathy
1-   patients with diabetic retinopathy

Comparison of Urine PCR and Ankle Brachial Index(ABI) between cases and controls

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	PCR	.023	.010	5.734	1	.017	1.024
	ABI	-1.219	1.798	.460	1	.498	.295
	Constant	-.153	1.987	.006	1	.939	.858

PCR: p value=0.017(<0.05), there exist a statistical significance between cases and controls.
ABI: p value=0.498(not <0.05), there was no statistical significance between the cases and controls.

Comparison of Biothesiometry value between the case and controls.

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BIO	.070	.037	3.551	1	.059	1.072
	Constant	-1.074	.618	3.020	1	.082	.341

P value=0.059(not <0.05), there was no statistical significance between the case and control group.

Comparison of Fundus changes(Diabetic Retinopathy) between the cases and controls

		FUNDUS	USG LIVER#
FUNDUS	Pearson Correlation	1	.294[*]
	Sig. (2-tailed)		.023
	N	60	60
USG LIVER#	Pearson Correlation	.294[*]	1
	Sig. (2-tailed)	.023	
	N	60	60

P value=0.023(<0.05), there exist a statistical significance between the cases and controls.

Once again, the study case group was divided based the grading of fatty liver into Grade 1, Grade 2 and Grade 3 by the USG finding and looked for an association of Urine PCR levels and Fatty Liver Severity.

ANOVA test between NAFLD grading and Urine PCR:

Source of variation	Sum of Squares	DF	Mean Square
Between groups (influence factor)	13088.6735	2	6544.3367
Within groups (other fluctuations)	34696.0332	27	1285.0383
Total	47784.7067	29	

F-ratio	5.093
Significance level	P = 0.013

Tukey-Kramer test for all pairwise comparisons

Fatty liver grade	n	Mean	SD	Different (P<0.05) from factor nr
(1)	11	70.5182	17.8908	
(2)	11	97.4273	51.7838	(3)
(3)	8	44.5750	25.8556	(2)

P=0.013(<0.05), therefore there exist a correlation between the Urine PCR and Degree of Fatty changes in the liver.

IV   Discussion

The purpose of the study was to find an association between micro and macro vascular complications with Non Alcoholic Fatty Liver Disease (NAFLD) in type 2 diabetes mellitus. Hence a case control study, which included 30 NAFLD cases and 30 controls was conducted in the Department of Diabetology , Department of Radiology and Department of Ophthalmology in our institution.

The exclusion criteria included Diabetic patients with obvious liver disease due to other causes (Hepatitis B, C), patients with a history of exposure to hepatotoxic agents like alcohol and others medications.

The cases and controls in the study were age matched with mean value of 54.50 in cases and 56.60 in controls.

The Mean Urine Protein to Creatinine ratio(PCR) which signifies the amount of proteinuria, was much higher in cases than the control group.

Mean PCR value in cases and controls were 73.46 and 49.01 respectively, with a p value = 0.017(<0.05) which should a statistical significance between the two groups, this is in accordance to the study made by Giovanni Targher(15).

Once again, when the study case group was divided based the grading of fatty liver into Grade 1, Grade 2 and Grade 3 by the USG finding and looked for an association of Urine PCR levels and Fatty Liver Severity, it should an increase in the disease status of Diabetic Nephropathy as the Severity of Fatty liver increased.

On Comparison of Fundus changes for Diabetic Retinopathy between the cases and controls, there was a positive correlation which was statistically significant with p value=0.023(<0.05), which is in accordance with study already done by Vijay et al.(14).

Mean ABI value in case and controls were 1.003 and 1.04 respectively with p value=0.498(not <0.05), there was no statistical significance found between the cases and control group, which was in contrary to the study made by Vijay et al(14).

Mean of Biothesiometry value between the cases and controls were 17.50 and 13.69 respectively, with p value=0.059(not <0.05), implying that there was no statistical significance between the case and control group, which is in contrary to the study made by Sureshet al(16). The reason might be Biothesiometry technique to measure the Diabetic Neuropathy was a subjective measurement, where the chances of error are more.

Therefore, detecting the presence of Fatty liver in Diabetic patients at an early stage by Ultrasonography could be used to assess and predict the adverse diabetic micro and macrovascular complications.

V   Conclusion

- NAFLD findings will be useful as a prognostic tool in the treatment of T2DM.
- Non-invasive ultrasonography to detect NAFLD can be used as an ideal screening tool to assess the degree of the micro and macro vascular complications existing in Type 2 DM patients.
- Periodic Ultrasound grading of liver for NAFLD might be used to find the progression and severity of T2DM and its adverse outcomes.
- Hepatic steatosis can be used as an early marker of Diabetes and its complications.

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