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RESEARCH ARTICLE

LIVER FIBROSIS ASSESSMENT IN DIABETESMELLITUS PATIENTSUSINGELASTOGRAPHY IN A TERTIARY CARE HOSPITAL

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Abstract

Introduction: Diabetesmellitusisoneofthemostcommondiseasewithanestimateofaround Diabetes 400millionpopulationaffectedworldwide.Diabetesisadiseaseofcomplications,bothacute and chronic. There is a wide range of liver manifestations associated with Diabetes. Many diabetic patientshave beendetectedwithfattyinfiltrationof liver,mainlymanifestedasNon-alcoholic fatty liver disease (NAFLD).In India ,NAFLD is emerging as an important cause of liverdisease.NAFLDpatientswithDiabeteshasincreasedchanceofdevelopingcomplications of chronic liver disease including liver fibrosis.Toassess hepatic fibrosis, liver biopsy is still theonlyreliable"goldstandard".However,thismethodisinvasiveandassociatedwithpossible risks and complications, hence non-invasive imaging methods like serum biomarkers, conventional ultrasound, ultrasound elastography are beingused for assessment of liver stiffness measurement(LSM).

Aims and Objectives: To studythepattern of significant liver fibrosis in diabetes mellitus patients with non alcoholic fatty liver disease usingtransient elastography. To determine the association of liver stiffness by elastography with other factors in diabetes mellitus patients.Tostudythecorrelationbetweennon-invasivescoresofNAFLDandliverstiffnessmeasure in patients with non alcoholic fatty liver disease usingtransient elastography.

Method: Cross sectional study was done in 108 patients with Diabetes& Fatty liver visiting SreeGokulam medical college between May 2021 & May 2022. Correlation was studied betweenliver stiffness byelastographywith other riskfactors. Cohen'skappacoefficient was used to find agreement between FIB4 Score, APRIScore,BARD Score and fibroscanresults .

Result: 42%ofmale patients(18)and38%offemalepatientshadF3&F4liverstiffnesswhile 19 patients had F1 & F2 liver stiffness. The mean age of the study population is 50.12 years. 79% of males and 61 % of females were found to be obese. Out of obese patients,45 % had significant liver stiffness. 95% of patients with F3/F4 stage of liver stiffness had

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elevated HbA1c(n=41)whichshowedasignificantcorrelation(p<0.02).ASTelevation hadasignificant correlation with significant fibrosis (p<0.05) .55% of elevated AST cases had F3/F4 liverstiffness.Cohen'skappacoefficientshowedsubstantialagreementbetweenresultsofFibroscan and APRI,BARD&FIB-4.**Conclusion:**Significantfibrosiswasdetectedmainlyinobesewithpoorglycaemic control&dyslipidaemia. Elevated liver enzymesalso had a significant correlation with significant fibrosis. Timely diagnosis of NAFLD and intervention is essential to reduce the risk of liver disease progressionespecially in diabetic patients.

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Introduction:-

Diabetesmellitusisoneofthemostcommondiseasewithanestimateofaround400 million populationaffected worldwide. Non-alcoholic fatty liver disease (NAFLD) is a hepatic condition characterized by abnormal fat accumulation in liver cells; histologicallyresemblingalcoholinducedliverdamage.NAFLDisthoughttoaffect~6–50%oftheadultpopulation,dependentonthepopulationstudiedandthemethodof assessment [7,8].Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher incidence amongst overweight/obese and diabetic/ prediabetic patients. The TrivandrumNAFLD cohortstudyshowed49.8%prevalenceoffattyliver,whichissignificantlyhigher thanthe global prevalence of25%. [9]Non-invasive alternatives include serum biomarkers, conventional ultrasound, ultrasoundelastography,magneticresonanceelastography,andmagneticresonance- based fat quantitation techniques for assessment of liver stiffnessmeasurement(LSM). Thefirst imaging modality used forthe screening of suspected NAFLD in diabetic patientsand which can evaluate fatty liver is conventional ultrasound.Butinordertocharacterizeliverfibrosis,ultrasoundelastographyseems apromisingnon-invasivetool.[15,16]Mostvalidatednoninvasivemethodshaveshown good accuracy in diagnosing patients with a significant degree of fibrosis (fibrosis expanding beyond the portaltract)[17].Identification of significant fibrosis (≥F2) has beenregardedasanimportantindicatortodetectadvancestageofliverfibrosiswhich is clinically relevant. Transient elastography (TE) is probably the most widely used noninvasivemethodinEuropeforassessingthedegreeofliverfibrosis(FibroScan)[18] **Transient elastography (Fibroscan® Echosens, Paris, France)**can help in quantitative assessment of liver fibrosis. Results are expressed in kilopascals (kPa) Hence, this study is done to assess the presenceof significant liver fibrosis using Transient Elastography in a cross section of our population as quantifying liver fibrosis in DM patients with NAFLD to determine prognosis and guide treatment decisions is an important part of the clinical workup.

Method:-

Study Design:
Cross sectional Study

Study Setting:
Department of General Medicine, SreeGokulam Medical College and Research foundation.

Studypopulation
PatientswithDiabetesmellitusvisitingDepartmentofGeneralMedicine ,SreeGokulam Medical College and Research Foundation between May 2021 and May 2022, who havebeen detected with Fatty liver in USG abdomenas a part of investigation.

Inclusion Criteria:
1.Patients above the age of 18 years diagnosed as diabetic (with WHO criteria)2. USG abdomen showing fatty liver.

Exclusioncriteria:
1.Patientswithchronicliverdiseaseofetiologyother than NAFLD. 2. Patients with history of hepatotoxic /steatogenicdrug intake.3.Pregnancy.4.Historyofalcoholconsumption>20gminwomen&>30gminmen.5.Measurement failure or unreliable measurements on TE6.Cardiac Failure NYHAIII& IV.5. Consent not given.

Sampling Technique:
Patients who match the inclusion and exclusion criteria andselected randomly during period of approximately one year, form the study group.

Studyperiod:
Aperiodof12months,startingfromMay2021toMay2022

Methodology:-

After approval from the Institutional ethics committee and obtaining informed written informed consent from each patient, History, Physical examination, as per the proforma was done in all patients. Diabetes confirmed by obtainingFastingandpostprandialbloodsugarandHbA1candasperWHOcriteria. They were screened for fatty liver with Ultrasound. Detailed history regarding duration of diabetes, history of drug intake , any other past illnesses weretaken. History of microvascular &macrovascular complications noted.Those diabetic patients with fatty liver were taken in to study group and assessed for non invasive score APRI, BARD score ,FIB-4 score & fibrosisof liver using Transient Elastography(Fibroscan,Echosens,Paris,France). Tests includingBlood count, LFT,RFT, Lipid profile, were done in all the patients.

Study Variables:
Age, sex, Dyslipidemia, BMI, Duration of DM, Haemoglobin, Fasting Blood glucose,Post Prandial Blood Glucose, HBA1C , Lipid profile, LFT & RFT parameters,findings in Ultrasound and transientElastography liver stiffness(in Kpa).

Dataanalysis:
Aftercollectingthedata,todeterminetheassociationbetween liver stiffness by elastography with other factors of T2DM, chisquare test was used.The necessary statistical tables constructed along with charts and diagrams.Pearson's correlation coefficient/ Cohen’s kappa correlation coefficient used to find strength of agreement between FIB4 Score,APRIScore,BARD Score andfibroscanresults.QuantitativedataexpressedasMean+SDandQualitativedata expressed in percentage.

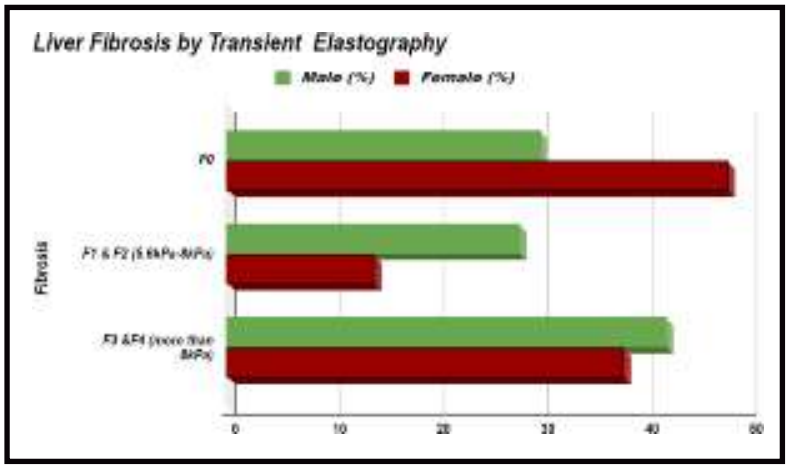
Results:-

108 patients, 65 females (60.2%) and 43 males (39.8%)were included.Fibro scan was done in all patients to assess significant liver fibrosis (>8kPa). 42% of male patients(18)and38%offemalepatientshadF3&F4liverstiffnesswhile19patients had F1 & F2 liver stiffness.Correlation was not significanthere.(p value=0.817)

Table:- Significantfibrosisassessment byTransientElastography.

Fibrosis	Male (%)	Female (%)
F0	30	48
F1 &F2 (5.6kPa-8kPa)	28	14
F3&F4 (morethan 8kPa)	42	38

Figure:- DLPprofilewithsignificantfibrosis.

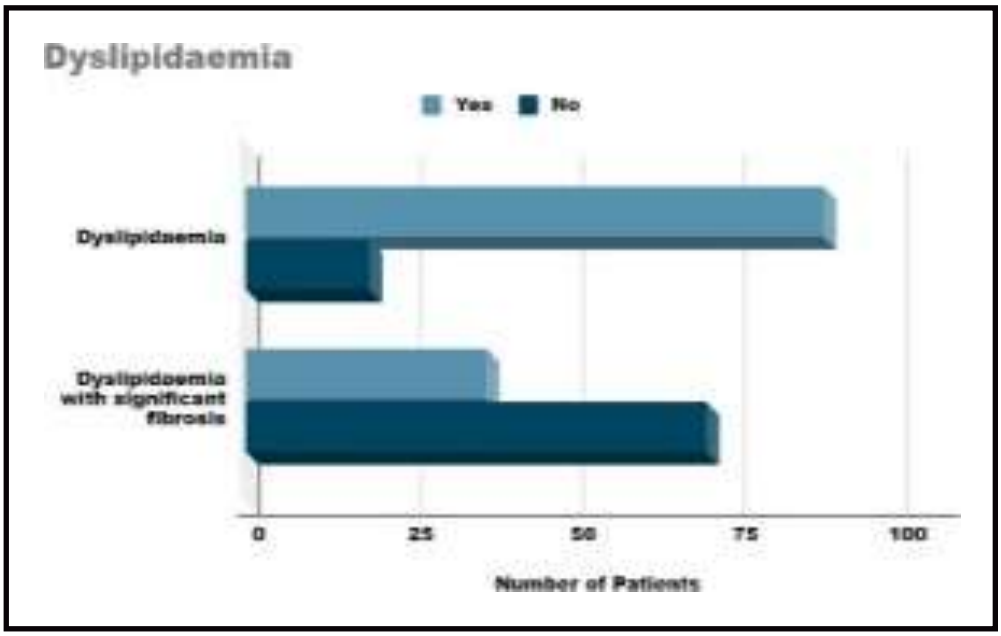


HypertensionProfile

43patientshadhypertension(39.8%).39.5%ofpatientshadsignificantfibrosisand hypertension.

DyslipidaemiaProfile

Dyslipidaemia was found in 82%of patients and 42% ofdyslipidaemic patients detected with significant fibrosis. Lipid profile showed TGs > 150mg/dL in 57 patients(m=30,f=27)with25of themdetectedforsignificantfibrosis.(44%).HDL<40mg/dLwasfoundinonly23%ofcases(n=25)but48%ofsuchcaseshad>F2 stage of liver stiffness. Correlation between dyslipidemia and fibrosis was found to be not significant(p value=0.078)



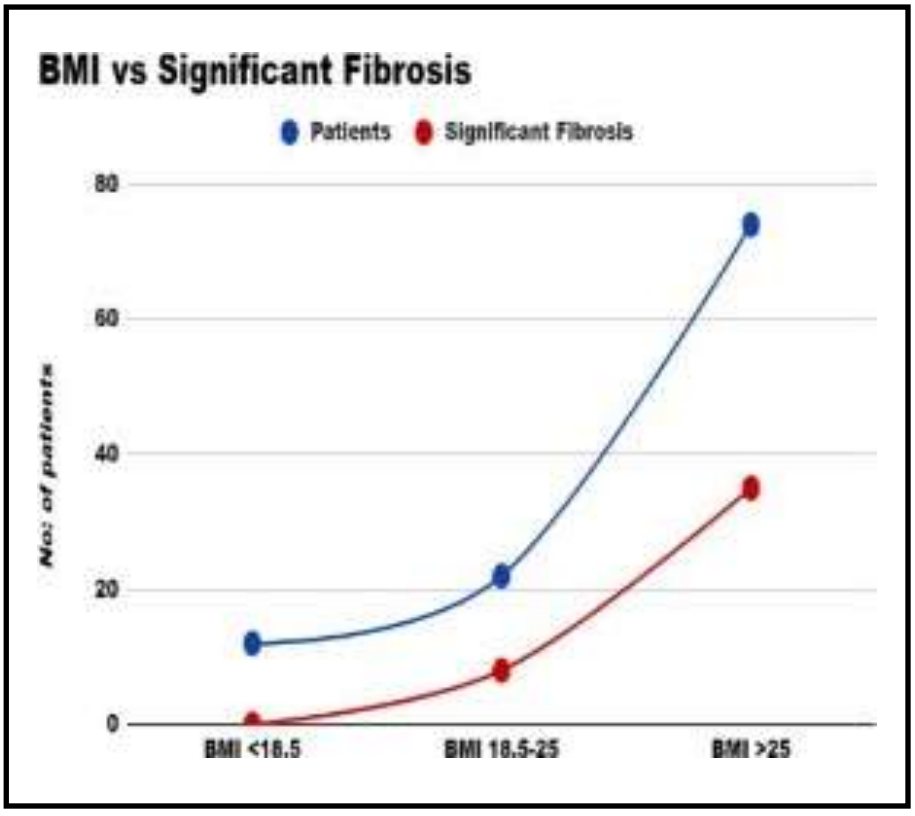
DLPprofilewithsignificantfibrosis.

Lipidprofile	mean	SD
TotalCholesterol	209.8	49.26
Triglycerides	170.6	76.62
LDL	133.9	40.34
HDL	46.12	9.20

BMIwasassessedinallpatients.79%ofmalesand61% offemaleswerefoundtobeobese. Out of obese patients,45 % had significant liver stiffness.

Table7.BMIprofile

BMI	Patients	Significant Fibrosis
BMI<18.5	12	0
BMI18.5-25	22	8
BMI>25	74	35



Glycaemiccontrol

HbA1cwasassessedinthestudygroupforglycaemiccontrol.MeanvalueofHbA1c was 8.6 . Values above 6.4 was noted in 95 patients which constituted 88% of the studygroup.95%ofpatientswithF3/F4stage ofliverstiffnesshadelevatedHbA1c (n=41)whichshoweda significantcorrelation(p<0.02).FBS>126mg/dL wasfound in 66.7% of patients (n=72) and 43% (n=31) of them had liver fibrosis.

CorrelationbetweenHbA1CandSignificantFibrosis

HbA1C	Fibrosis absent(n)	Fibrosis present (n)	Chi-square
Normal Elevated	13 54	2 (4.7) 41(95.3)	pvalue:<0.02

FBS profile.

FBS	Patient s	Significant Fibrosis
FBS <100 mg/dL	22	4
FBS 100-126mg/dL	14	8

Liver enzymes

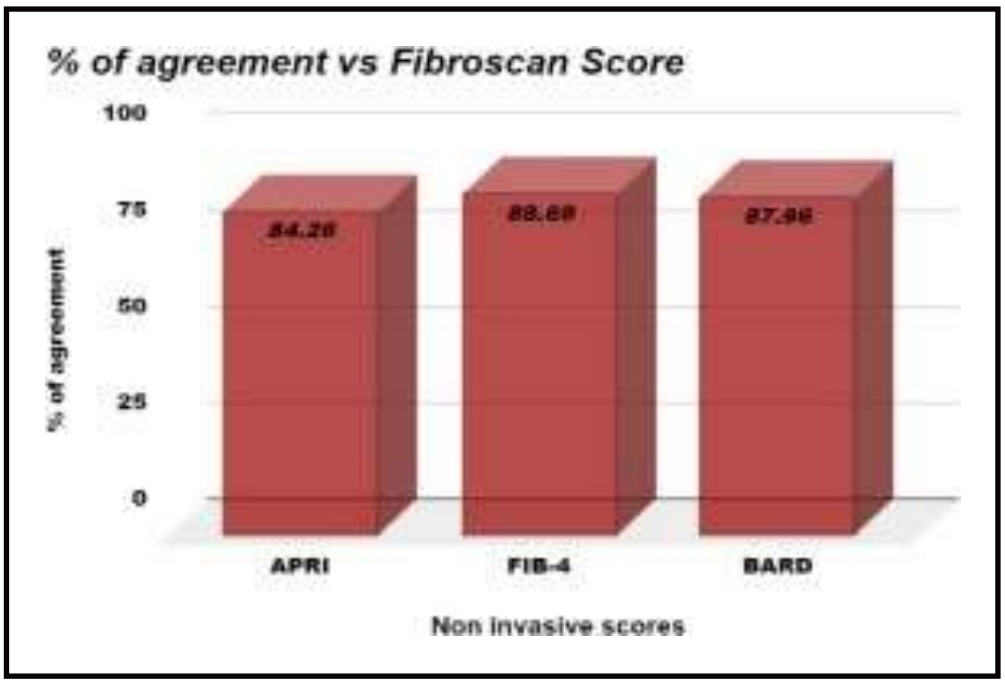
Liver enzymes were studied in the group to assess whether elevation in enzyme profile is a risk factor for liver fibrosis. Even though fatty liver was an inclusion criteria, elevation of ALP was not noticed. But, AST & ALT were elevated in 45% &30%ofpatientsrespectively.Also,ASTelevationhadasignificantcorrelationwith significant fibrosis ($p<0.05$) .55% of elevated AST cases had F3/F4 liver stiffness.

Table:- CorrelationbetweenASTandSignificantFibrosis.

AST	Fibrosis absent(n)	Fibrosis present(n)	Chi-square
Normal	59	16	pvalue:<0.05
Elevated	22	27	

NonInvasivescores

Number ofsignificant fibrosis casesdetected by Fibroscan was studied in relation to the results from noninvasive scores like APRI score, FIB-4 score and BARD score to find the strengthofagreementbetweentheseresults.Cohen'skappacoefficientwas usedand found substantial agreement between Fibroscan and all 3 non invasive scores



Discussion:-

Increasing prevalence of diabetes mellitus, and associated fatty liver changes (NAFLD) has become a major cause for significant liver fibrosis. Alagesan et al, showed a prevalence of 55%amongmalesand39%amongfemales with Diabetes and NAFLD forliver stiffness. In our study, significant fibrosis (>8kPa) was found in 42% of males and 38% among females who had both Diabetes and NAFLD. Yen YH et al observedelevated BMI as an independent risk factor associatedwithclinicallyrelevantfibrosisinpatientswithDMandNAFLD. Our study also foundthat significant fibrosis increased withincreased BMI. Elevated glucose and hyperinsulinemia are among the potential biological factors affectingliver fibrosis progression.Watt GP et alstatedthat elevated HbA1c is an importanttriggering point forscreening of hepatic fibrosis.Present study corroboratesthefindingsofpreviousssimilarstudieswithhighHbA1cvalueshaving significantcorrelation($p<0.001$) with increase in liver stiffness.43% of cases with HbA1c>6.4hadsignificantfibrosisinthestudygroup.Mikolasevicetal&Lallukka S et al have found that liver enzymes, are associated with liver fibrosis.Elevations inASThasalsobeen associatedwithadvanced fibrosisdueto delayed clearanceofASTthanALTandassociatedmitochondrialinjury.SanyalDetalfoundthatcaseswithNAFLDhadsignificantlyhigherALT,ASTthanthosewithout NAFLD.Current study also points out that liver enzymes especially ASThas significantcorrelation($p<0.05$)with increase inliver stiffness. Mendez et al stated that systemichypertension and dyslipidemia significantly increased the risk for advancedliverfibrosisespeciallywhenpatientswereolderandhavelowerlevelsof platelet count and albumin. Our study also found a strong association with 86% of significant fibrosis cases having dyslipidemia but only 39% had systemic hypertension.Also, platelet count and albumin levels were not on the lower side as found in the reviewed study. Lin H et al identifieda U-shaped relationship between theurealevelandliverfibrosisespeciallyinpatientswithChronicLiverDiseaseand found low urea level as a potential marker and predictor for advanced liver disease. But, our study group had no reported cases of low urea and hence could not corroborate with result of referred study. Liver fibrosis assessment has nowadays almost entirely been performed by noninvasive methods like transient elastography (TE), or biochemical markers and scoring systems, such as the APRI score, BARD score, FIB-4 score etc. The main advantage of these scores is availabilityat a low costandsimpletouse.However,TEisnotwidelyavailableandcostly,whileAPRI and other scores have been used reliably. Based on evidence collected from systematicreview,theWHOguidelinesrecommendedFibroScanandAPRIasmost usefultestsfortheassessmentoffibrosisinresource-limitedareas.RungtaS,Kumari S, Verma K, et al. did a comparative analysis of these scoreswith fibroscan measurement , found that APRI and FIB-4 are significantly able to assess liver stiffness. We also studied the correlation between these noninvasive scores and fibroscanassessmentandfoundsignificantlevelofagreement.Finally,limitationsof thisstudyneedmentionsuchasthecross-sectionaldesignwhichavoidsacausaland temporal relationship between Liver stiffness progression and associated variables. Also,studygrouphadonlyasmallnumberofpatientswithsignificantfibrosiswhich indicates the necessity of conducting a prospective study in a larger sample population.

Conclusion:-

SignificantfibrosiswasassessedinDiabeticpatientswithNAFLDandwasdetected mainlyinthosewhohadobesity,poorglycaemiccontrol,&dyslipidaemia.Elevated liver enzymesalso had a significant correlation with development of significant fibrosis.Liver stiffness assessment can be effectively done using Transient Elastography scan eliminating the need for liver biopsy. Non invasive scores like APRI score, BARD score & FIB-4 score has substantialstrength of agreement with Fibroscan results in assessing significant Fibrosis.

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