Original Article

Non-alcoholic fatty liver disease and diabetic retinopathy: Is there an association?

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Abstract

Background: Studies have not proven whether an association exists between diabetic retinopathy (DR) and non-alcoholic fatty liver disease (NAFLD). The reports from various parts of the world have not used uniform criteria, and hence, results are inconclusive. Both DR and NAFLD are common conditions encountered in primary care. **Methods:** A total of 130 patients with type 2 diabetes from the medical wards of a tertiary care hospital were enrolled. After documentation of clinical and biochemical data, they underwent ultrasonography (USG) of the abdomen and fibroscan grading of liver. Retinopathy was assessed and classified as per the Early Treatment Diabetic Retinopathy Study. **Results:** The mean age of the patients included in the study was 46.5+/-8.8 with 55% of the participants being male and 45% female. The mean HbA1c was 7.168+/2.4. The association between DR and hepatic fibrosis was assessed by fibroscan (p 0.003) and USG (p 0.001) and was significant on univariate analysis. Multivariate analysis did not confirm this. There was no association between increasing grades of either condition. Although fibroscan and USG significantly concorded in diagnosing NAFLD, fibroscan diagnosed more cases as compared to USG (83 vs 73). **Conclusion:** Larger studies should be conducted to conclusively determine the association in order to investigate pathogenetic factors and treatment strategies.

Keywords: Diabetic retinopathy, microvascular complications, non-alcoholic fatty liver disease

In the past decade, non-alcoholic fatty liver disease (NAFLD) emerged as the most common aetiology of liver disease after being 'hidden" for a long period.[1] It is well recognised now that NAFLD has strong connections with obesity and its associations.[2] The estimated prevalence of NAFLD is above 60% in patients with diabetes and a half of this in general population.[3] This condition may be harbinger of metabolic derangements and more severe liver diseases, even leading to hepatocellular carcinoma.[4]

NAFLD is considered to be the hepatic manifestation of metabolic syndrome, and the coexistence of NAFLD and type 2 diabetes mellitus (DM) is over 70% in some studies.[5] The presence of NAFLD is known to confer an increased macrovascular risk.[6] However, the relationship between microvascular disease and NAFLD is not so well documented. The mechanisms postulated linking these include release of pathogenic modulators like cytokines or reactive oxygen species.[7] There have been only very few published reports on this topic which have not conclusively proved or disproved an association between these two conditions Diabetic retinopathy (DR) is the most common cause of preventable blindness with an estimated prevalence of 21.7%.[8] Studies performed in Indian population have also been inconclusive.[9-11] A recent meta-analysis to identify the association between NAFLD and DR comprising nine studies from different parts of the world concluded that there was no association [odds ratio (OR) = 0.94, 95% confidence interval (CI)].[12] However, the authors observed that there is a high level of heterogeneity in the

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populations studied with an r2 of 0.96. They postulated that the differing associations may be attributed to regional differences in insulin resistance and secretion. It is thus important to confirm any association with or contribution to the presence or severity of retinopathy by NAFLD in order to identify and treat any attributable risk factors. It is also to be noted that the studies included in the meta-analysis documented NAFLD based on ultrasound scan finding and not fibroscan scores. NAFLD and DR are frequently diagnosed in a primary care, both of which have sinister long-term complications. An association between the two, if established, would be an indication to screen for the other if one of these is detected. Hence, this study aimed to assess the association between NAFLD and retinopathy and also to document any correlation of the severity of retinopathy with grades of NAFLD using ultrasound and fibroscan.

Methodology

Study setting: In-patient and out-patient departments of a tertiary care teaching hospital.

Study participants: Adult patients aged 18 years and over with type 2 DM of over 5 years with alcohol intake less than 20 g per day were enrolled. Pregnant ladies and those on with hepatotoxic drugs and/or those with any known liver disease were excluded.

Sample size: Based on previous studies on the prevalence of DR and NAFLD in India and that which reported an association between NAFLD and microvascular disease, a sample size of 97 was estimated at 10% precision and 95% confidence.[9,13,14]

Study procedure: After obtaining informed consent demographic details, history of complaints and conditions were obtained, followed by relevant examination. Bio-chemical tests including fasting blood glucose, post-prandial blood glucose, glycated haemoglobin (HbA1c), fasting lipid profiles, and liver function tests were assayed in the NABL (National Accreditation Board for Testing and Calibration Laboratories) accredited laboratory attached to the institution.

Fundus examination for retinopathy was performed by a qualified ophthalmologist and classified according to ETDRS (Early Treatment Diabetic Retinopathy Study) as no DR, mild NPDR, moderate NPDR, severe NPDR, and PDR.[15]

Utrasound scan of the liver was performed by a certified radiologist, and fatty liver was graded as below[16]:

Grade I: increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.

Grade II: increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm.

Grade III: increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm fibroscan.

Transient elastography was performed and graded by a qualified gastroenterologist experienced in the procedure. The stiffness score in kPa (kilopascal) was documented with measurements performed on the right lobe of liver at a depth of up to 65 mm below the skin. These were scored from F0 to F4.[17]

Statistical analysis

The data were analysed using SPSS version 22 with appropriate statistical tools (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) Descriptive statistics was reported using mean and SD for the continuous variables and number and percentages for the categorical variables. Association with clinical parameters was performed using Chi-square test or independent *t*-test as appropriate. Multiple regression analysis was used to ascertain the independent association between NAFLD and DR. A '*P* value' less than 0.05 was considered as statistically significant.

Ethics approval

The study proposal and protocol were reviewed and approved by the Institutional Ethics Committee (Ref.No. 275/2017).

Results

A total of 130 participants were enrolled into the study (M:F = 72:58). The baseline characteristics and bio-chemical measurements are listed in Table 1. Eighty-two (63%) were diagnosed to have retinopathy (M: 44; F: 38). Seventy-three (56.2%) had fatty liver, with 50 grade 1, 22 grade 2, and one participant having grade 3 fatty liver by ultrasound [Table 2].

There was a significant association between presence of fatty liver by ultrasound and presence of retinopathy (*P* 0.02). However, on comparing grades of retinopathy with grades of fatty liver, no association was detected. Fibroscan-diagnosed NAFLD also showed a significant association with the presence of retinopathy (*P* 0.003) [Table 3]. On comparing grades of NAFLD with grades of retinopathy, there was no significant association.

Fibroscan and ultrasound comparison was noted to have a significant association ($P = 0.001$) [Table 4]. As compared to ultrasound scan, fibroscan detected ten more cases with increased liver stiffness.

On multiple regression analysis performed with age, gender, duration of T2 DM, HbA1c value, and presence/absence of dyslipidaemia/HTN as variables, the coefficient of correlation of T2-DM, HbA1C value, and presence/absence of direct relation between DR and NAFLD were determined.

Discussion

This cross-sectional study was performed in a multi-speciality centre over a period of 2 years. The study assessed the relationship between fatty liver and DR. There was a significant

Table 1: Baseline characteristics

Variable	Male	Female	Total
Age (mean±SD)	47.4 +/- 12.2	45.2 +/-11.8	46.8+/-11.0
HbA1C (mean±SD)	7.8 +/- 3.2	6.18 +/- 2.2	7.168 +/2.4
BMI (mean±SD)	22.1 +/- 3.2	20.3 +/- 2.3	21.3 +/- 3.1
Fasting glucose (mean±SD)	123.3 +/- 34.0	111.2 +/- 22.2	118.2+/-24.0
Total cholesterol (mean±SD)	180.4 +/- 32.7	170.7 +/- 23.2	177.5+/-26.3
Triglycerides (mean±SD)	150.5 +/- 22.0	125.6 +/- 12.2	143.3+/-14.4
AST (mean±SD)	46.1 +/- 12.3	40.2 +/- 2.2	43.5+/-8.6
ALT (mean±SD)	41.2 +/- 12.1	38.7 +/-9.7	40.7=/-10.0
Duration of diabetes (years±SD)	8+/-1	6+/-1	7.5+/-1

Table 2: Association between fatty liver and DR (*P* 0.01)

Ultrasound image	Retinopathy + (*n*)	Retinopathy – (*n*)	Total (*n*)
Fatty liver +	30	27	57
Fatty liver _	18	55	73
Total	48	82	130

Table 3: Association between fibroscan grade and DR (*P* 0.003)

Fibroscan Grade	Retinopathy+	Retinopathy -	Total
No fibrosis	22	25	47
Fibrois +	60	23	83
Total	82	48	130

Table 4: Correlation between ultrasound and fibroscan (*P* 0.001)

Fibroscan USG	F0 grade	F1 grade	F2 grade	F3 grade	F4 grade
No fatty liver	47	10	0	0	0
Grade 1 fatty liver	0	50	0	0	0
Grade 2 fatty liver	0	0	22	0	0
Grade 3 fatty liver	0	0	0	1	0

association between DR and fatty liver by ultrasound, which was reiterated on comparing DR and fibroscan scoring. However, grades of retinopathy were not associated with the grades of fatty liver by ultrasound or to liver stiffness assessed by fibroscan. Although there was concordance between USG and fibroscan gradings, fibroscan picked up more cases of liver stiffness as compared to USG.

The association between NAFLD and DR has been studied by previous studies.[7,18,19] A study from Iran explored the association between NAFLD and retinopathy in individuals with and without diabetes.[20] The presence of DR was photographed and documented, and liver stiffness was measured by an experienced radiologist using ultrasound scan. This study concluded that the presence of NAFLD was not associated with DR even when adjusted for age, gender, race, WC, lipids, BP, and HbA1C, and they concluded that NAFLD is not a contributory factor for DR. In contrast, Targher *et al*.[7] reported a significant association between proliferative DR and NAFLD in patients with type 2 DM.[21] In their study of 2103 patients, NAFLD was associated with proliferative and non-proliferative DR in both uni- and multivariate analysis. The authors postulated that the release of some mediators of inflammation like advanced glycation products, RP, and IL-1 may be the causative factors of vascular injury in various tissues. However, a Korean study with 929 participants published an inverse relationship between these two conditions.[18] The reason for this difference in results was deduced to be due to the differing characteristics of the study populations. The meta-analysis mentioned earlier in the paper did not find an OR favourable to the association between DR and NAFLD.[12] They had commented on the heterogeneous nature of the included publications and the possibility of regional differences in involved factors. Although the results of the present study on multivariate analysis negate such an association, univariate analysis showed some. Hence, large prospective studies are required to conclusively decide on the risks conferred by NAFLD on DR.

The main drawback of the study is that it was conducted on 130 patients and was only powered to detect the relationship between the presence of DR and NAFLD and not to study the severity of one versus another. Further, no markers of either condition were measured, and the groups with and without NAFLD were different in terms of age and no biopsies were performed to confirm the diagnosis either.

An association between NAFLD and DR may have implications in the care of patients with either of the conditions. An association between hepatocellular carcinoma and DR has been reported by Azuma *et al*.[22] In this study, multivariate analysis identified DR (OR 8.654; $P = 0.017$) as an independent factor that was significantly associated with the development of HCC jn patients with NAFL. For predicting the development of HCC, the area under the receiver operating characteristic curve of DR was significantly higher than that of diabetes (0.731 vs. 0.615; $P < 0.001$). DR as well as liver fibrosis is a risk factor that associates with the development of HCC in NAFLD patients. Therefore, NAFLD patients with DR should undergo careful screening for HCC as DR may precede the diagnosis of DM and patients with NAFLD should be assessed for DM and also DR.[23] The exact nature of the relationship can be established only through studies involving a large number of patients. The complex interplay of DR and NAFLD, with their increasing prevalence in Indian population, warrants further evaluation to

explore the application of this knowledge in the management of both entities.

Conclusion

There may be an association between NAFLD and DR. The etiopathogenetic connection between the two conditions needs to be established along with the mediators of such association to clearly understand the pathophysiology.

Although our study did not find a direct association between NAFLD and DR, it clearly shows that patients with diabetes have a higher degree of liver stiffness, many of whom remain undetected by routine liver enzyme tests and USG. Hence, screening for DR when NAFLD is diagnosed and vice versa will be useful in the early detection of these conditions in primary care. The interactions and dynamics of DM and NAFLD, with their increasing prevalence in Indian population, warrant further evaluation to investigate the application of this knowledge in the management of both entities. Our study has attempted to add on to the very limited literature on NAFLD and retinal microvascular disease.

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Conflicts of interest

There are no conflicts of interest.

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