TO STUDY THE PREVALENCE OF FATTY LIVER AND RETINOPATHY IN NEWLY DIAGNOSED CASES OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

The epidemic of Type 2 diabetes mellitus (DM) is assuming significant proportions in developing countries such as India. Diabetics have an increased risk of developing a number of serious problems affecting heart, blood vessels, kidneys, eyes and nervous system. Since prediabetic stage may last for 4-7 years before overt diagnosis of type 2 diabetes mellitus is established, metabolic effects of insulin resistance and beta cell failure can manifest as non-alcoholic fatty liver or macro or microangiopathies. The aim of this study was to define the prevalence of non-alcoholic fatty liver disease (NAFLD) and diabetic retinopathy (DR) in the newly detected cases of T2DM.

MATERIALS AND METHODS

This study was conducted on 100 newly diagnosed cases of T2DM of either sex. All patients after routine investigations subjected to indirect ophthalmoscopy by expert ophthalmologists and ultrasonography by a radiologist.

RESULTS

Of 100 patients in our study, 48% had fatty liver. Out of which 30 had mild, 16 had moderate and 2 had severe NAFLD. Diabetic retinopathy was present in 6 patients. There was no significant correlation seen between DR and NAFLD.

CONCLUSION

Efforts should be directed towards early screening of NAFLD and diabetic retinopathy in patients of diabetes to prevent and minimise irreversible damage.

KEYWORDS

Diabetes Mellitus, Non-alcoholic, Fatty Liver, Retinopathy.

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BACKGROUND

Diabetes mellitus (DM) is widespread and currently the most common endocrine disorder around the world. It comprises of a group of common metabolic disorders that share the common phenotype of hyperglycaemia.[1] The epidemic of DM, in particular type 2 DM (T2DM), is assuming significant proportions in developing countries such as India. The International Diabetes Federation (IDF) has projected that the number of people with diabetes in India would rise from 65.1 million in 2013 to 109 million in 2035.[1]

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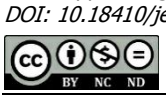

The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, higher waist circumference despite lower body mass index (BMI), lower adiponectin and higher levels of highly sensitive C reactive protein. This phenotype makes Asians more prone to diabetes and premature coronary artery disease.[2]

The onset of type 2 diabetes is often silent and insidious. Pathogenic processes causing type 2 diabetes range from autoimmune destruction of the β cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Diabetes mellitus is characterised by asymptomatic phase between actual onset of hyperglycaemia and clinical diagnosis which has been estimated to last at least 4-7 years. The asymptomatic phase of hyperglycaemia accounts for the relatively high prevalence of complications at initial presentation.[3,4]

People with diabetes have an increased risk of developing a number of serious problems affecting heart and blood vessels, kidneys, eyes, nervous system and also

develop serious infections. Since prediabetic stage last for 4-7 years before overt diagnosis of type 2 diabetes mellitus is established, metabolic effects of insulin resistance and beta cell failure can manifest as non-alcoholic fatty liver or macro or microangiopathies.

The onset of diabetes among Indians is about a decade earlier than their western counterparts and this has been noted in Asian Indians in several studies.[5] T2DM in Indians differs from that in Europeans in several aspects: The onset is at a younger age, obesity is less common, and genetic factors appear to be stronger. The younger age of onset implies that these subjects develop diabetes in the most productive years of their life and have a greater chance of developing complications.

The aim of this study is to define the prevalence of non-alcoholic fatty liver disease (NAFLD) and diabetic retinopathy (DR) in the newly detected cases of T2DM. This information would highlight the need of screening all newly diagnosed cases of T2DM irrespective of whether the symptoms and signs of hyperglycaemia or target end organ damage are evident on initial presentation or not. An early diagnosis and treatment would then help reduce disease-related morbidity and mortality.

NAFLD is clinicopathological condition that is characterised by deposition of lipid in the hepatocytes, where the mildest form of the disease being simple steatosis and in the most extreme forms it can cause hepatocellular failure or hepatocellular carcinoma. Non-alcoholic fatty liver is emerging as a leading cause of liver disease globally on the background of increasing prevalence of Diabetes and Obesity.[6] NAFLD is now considered as the hepatic component of the metabolic syndrome, both risk and severity of which increase with the number of components of the metabolic syndrome (obesity, insulin resistance, dyslipidemia). Compared with non-diabetic individuals, people with T2DM are at increased risk of developing NAFLD and have a higher risk of developing fibrosis and cirrhosis.[7-10] Another study showed that NAFLD was independently associated with an increased prevalence of chronic kidney disease and retinopathy in T2DM patients.[11]

There are few studies addressing specifically NAFLD in diabetic patients. Hence, new data are still required in order to better clarify the prevalence and clinical spectrum of NAFLD in this specific population. The prevalence of NAFLD, its correlation with diabetic retinopathy at the time of diagnosis of T2DM was studied in the present study.

Diabetes is known to cause microangiopathy and affects small calibre vessels leading to end organ damage like DR. It may even be present at the time of diagnosis of type 2 diabetic patients, consistent with the usually long duration of subclinical hyperglycaemia in such patients and more than 60% of type 2 diabetic patients will have some degree of retinopathy after 20 years of onset of diabetes.[12] Good control of blood glucose, blood pressure and blood lipids reduce a person's risk of developing retinopathy.[13] While the prevalence of DR in some populations is alarmingly high, active screening for this complication has been effective in reducing rates of severe diabetes-related eye damage.

Aims and Objectives

1. To study the prevalence of fatty liver in newly diagnosed cases of type 2 diabetes mellitus.
2. To study the prevalence of retinopathy in newly diagnosed cases of type 2 diabetes mellitus and to grade it.

MATERIALS AND METHODS

This study was conducted on 100 newly diagnosed cases of T2DM, of either sex attending the OPD or admitted in the Guru Nanak Dev Hospital/allied group of Hospitals attached to the Government Medical College, Amritsar for a period of two years. A written informed consent was taken from all the patients or the surrogate informer of the patients prior to including them in the study. Alcoholics, patients with hypertension, chronic renal failure, hypothyroidism, pre-existing liver disease (Cirrhosis, HBsAg/AntiHCV positive) were excluded from the study.

The patients were then evaluated under the following protocol-

- Detailed history
- Complete physical examination

BMI
Liver Function Test
HbA_{1C}
Fasting and Postprandial blood glucose

- Fasting Lipid profile
- Renal Function Test
- Thyroid profile
- Ultrasound abdomen
- Ophthalmologic examination

All patients were subjected to indirect ophthalmoscopy by expert ophthalmologists and four field retinal photographs were taken with fundus camera wherever needed. Grading of DR was done according to the ETDRS classification.

Biochemical Evaluation- Liver function tests and lipid profile were done after keeping the patient fasting for a minimal period of 8-10 hours. Blood samples were obtained under fasting condition and the following tests were performed using standard laboratory methods: Random/fasting blood sugar, HbA_{1c}, alanine ALT, AST, Serum albumin, total bilirubin, alkaline phosphatase, cholesterol, triglycerides, HDL, LDL, VLDL and Thyroid function tests.

Imaging Studies- Abdominal ultrasound was done in fasting state by experienced radiologists from Radiology department. The sonographic evaluations were carried out using real time scanner, Toshiba, with multi frequency transducer (3.5 and 7 MHz). After keeping the patient fasting overnight for a minimal period of 8-10 hours, so as

to limit bowel gas formation and to avoid gall bladder contraction. Ultrasound examination was carried out with the patient in supine and right anterior oblique position with coupling agent in the form of jelly, used for proper skin contact between the probe and skin. Scanning parameter used the default setting of the machine for the organ of interest i.e. the Liver, Spleen, Kidney. Liver was scanned in all planes to look for any evidence of fatty infiltration.

Staging of Steatosis

1. Mild- Minimal diffuse increase in the hepatic echogenicity: normal visualisation of the diaphragm and intrahepatic vessel borders.
2. Moderate- Moderate diffuse increase in the hepatic echogenicity. Slightly impaired visualisation of diaphragm and intrahepatic vessels.
3. Severe- Marked increase in echogenicity, poor penetration of the posterior segment of the right lobe of liver. Poor or non-visualisation of the diaphragm and intrahepatic vessels.

Statistical Analysis- Statistical analyses were carried out using Graphpad Software. Results were expressed as mean ± standard deviation. Significant differences between groups were evaluated using the Student t-test, χ^2 test wherever appropriate.

Observations- 100 patients of either sex with new onset of T2DM were included in the study. All patients were more than 40 years of age. Guru Nanak Dev Hospital is situated in the centre of the city, so we receive a mixture of both urban and rural population. Of the total 100 patients, 70 were female and 30 were male.

Total Number of Patients	Male	Female
100	30	70
Table 1. Gender wise Distribution of the Study Population		

100 patients with new onset of T2DM and age ≥ 40 years were included in this study. The maximum age was up to 65 years.

Age Group	Number of Patients
40-45	25
46-50	23
51-55	26
56-60	23
61-65	3
Table 2. Age wise Distribution of Patients	

The above observation showed that most of the patients with new onset T2DM belong to the age group 40-60 yrs. The average age at the time of diagnosis of T2DM was 51.35 ± 6.57.

All the patients were subjected to ultrasound examination of the abdomen to look for the presence or absence of fatty liver.

Total No. of Patients	NAFLD	Normal Ultrasound
100	48	52
Table 3. Prevalence of NAFLD in the Study Group		

The above observation showed that the prevalence of NAFLD in the study group was 48%.

Age Group	Total Number of Patients	Patients with NAFLD	Prevalence
40-45	25	9	36.0%
46-50	23	10	43.47%
51-55	26	13	50.0%
56-60	23	14	60.86%
61-65	3	2	66.67%
Table 4. Age Wise Distribution and Prevalence of NAFLD			

Age	Total No. of Patients	Patients with NAFLD	Prevalence
Up to 50 yrs.	48	19	39.58%
Beyond 50 yrs.	52	29	55.77%

The above observation showed that the prevalence of NAFLD was higher in those more than 50 years of age as compared to 40-50 age group i.e. the prevalence of NAFLD increased as the age group increased.

Patients with NAFLD were further categorised as having mild, moderate, or severe disease depending on the ultrasound criteria.

	USG grade of severity		
	Mild	Moderate	Severe
No. of Patients	30	16	2
Table 5. Severity of NAFLD in Patients based on Ultrasonography			

The above observation showed that majority of the patients having NAFLD at the time of diagnosis of T2DM had mild-moderate grade of disease.

BMI of all the patients was recorded using weight in kgs and height in metres using the standard measuring tape and weighing machine.

Variable	NAFLD Group	Non-NAFLD group	p value
BMI	27.24 ± 2.07	25.55 ± 1.47	<0.0001
Table 6. Association of BMI with NAFLD			

The above observation showed that the average BMI in NAFLD group was 27.24. This was significantly higher than average BMI in Non-NAFLD group, p value being <0.0001.

Groups	N	BMI	Comparison	p value
Normal	52	25.55 ± 1.47		
Mild NAFLD	30	26.71 ± 2.31	Mild vs. Normal	0.0068
Moderate NAFLD	16	28.01 ± 1.21	Moderate vs. Normal	<0.0001
Severe NAFLD	2	30.50 ± 1.31	Severe vs. Normal	<0.0001
Table 7. Comparison of BMI with Severity of NAFLD				

The above observation showed that severity of the NAFLD significantly increased with increase in BMI. (p value <0.0001).

Variable	NAFLD Group	Non-NAFLD group	p value
Serum triglycerides	183.75 ± 52.14	153.12 ± 53.23	0.004

Table 8. Association of Serum Triglyceride Levels with NAFLD

The above observation showed that the average serum triglyceride levels in the NAFLD group was 183.75 and that in non-NAFLD group was 151.19. This difference in the average value of triglyceride levels in the two groups was statistically significant (p value was <0.05.).

Groups	N	S. Triglycerides (Mean ± SD)	Comparison	p value
Normal	52	151.19 ± 50.25		
Mild NAFLD	30	170.83 ± 43.08	Mild vs. Normal	0.0767
Moderate NAFLD	16	198.69 ± 51.86	Moderate vs. Normal	<0.0001
Severe NAFLD	2	308 ± 36.76	Severe vs. Normal	<0.0001

Table 9. Comparison of Serum Triglyceride Levels and Severity of NAFLD

The above observation showed that the severity of NAFLD increased significantly with increase in the serum triglyceride levels (p value <0.0001).

Variable	NAFLD Group	Non-NAFLD group	p value
SGOT	45.25 ± 17.13	32.46 ± 10.94	<0.0001

Table 10. Association of SGOT Levels with NAFLD

The above observation showed that the average SGOT level in the NAFLD group was 45.25 and that in non-NAFLD group was 32.46. This difference in the average value of SGOT levels in the two groups was statistically significant (p value was <0.05).

Groups	N	SGOT Levels (Mean ± SD)	Comparison	p value
Normal USG	52	32.65 ± 10.94		
Mild NAFLD	30	35.67 ± 7.44	Mild vs. Normal	0.183
Moderate NAFLD	16	58.19 ± 15.06	Moderate vs. Severe	<0.0001
Severe NAFLD	2	85.50 ± 10.60	Severe vs. Normal	<0.0001

Table 11. Comparison of SGOT Levels and Severity of NAFLD

The above observation showed that as the severity of the NAFLD increased, the SGOT levels also increased, with p value <0.0001 showing statistical significance.

Variable	NAFLD group	Non-NAFLD group	p value
SGPT	53.23 ± 17.36	38.85 ± 14.71	<0.0001

Table 12. Association of SGPT Levels with Severity of NAFLD

The above observation showed that the average SGPT level in the NAFLD group was 53.23 and that in non-NAFLD group was 38.85. This difference in the average value of SGPT level in the two groups was statistically significant as the p value was <0.05.

Groups	N	SGPT Levels (Mean ± SD)	Comparison	p value
Normal	52	38.85 ± 14.71		
Mild NAFLD	30	45.87 ± 12.06	Mild vs. Normal	0.0294
Moderate NAFLD	16	62.50 ± 16.85	Moderate vs. Mild	<0.0001
Severe NAFLD	2	89.50 ± 7.78	Severe vs. Normal	<0.0001

Table 13. Comparison of SGPT Levels with Severity of NAFLD

The above observation showed that as the severity of the NAFLD increased, the SGPT levels also increased, with p value <0.0001 showing statistical significance.

All the patients were subjected to indirect ophthalmoscopy to look for the presence or absence of retinopathy and following observations were made.

Total Number of Patients	Retinopathy Present	Normal fundus
100	6	94

Table 14. Retinopathy in the Study Group

The above observation showed that the prevalence of DR in patients with newly diagnosed T2DM was 6%.

Age Group	Number of Patients with Retinopathy	Total Number of Patients
40-45	1	25
46-50	1	23
51-55	2	26
56-60	1	23
61-65	1	3

Table 15. Age Wise Distribution of Patients with Retinopathy

Age Group	Number of Patients with NAFLD	Total Number of Patients	Prevalence
Up to 50 yrs.	48	2	4.17%
> 50 yrs.	52	4	7.70%

The above observation showed that four of the six patients with DR were over 50 years of age.

	NPDR				PDR	
	Mild	Moderate	Severe	Very Severe	NVD	NVE
Number of Patients	6	-	-	-	-	-

Table 16. Ophthalmoscopic Grading of DR

Variable	Retinopathy seen	Normal fundus	p value
Serum triglycerides	276.83 ± 24.93	162.79 ± 48.26	<0.0001

Table 17. Association of Serum Triglyceride Levels with Retinopathy

The above observation showed that the average serum triglyceride level in patients with DR was 276.83 mg/dL and that in those without retinopathy was 162.79 mg/dL. This difference in the average value of triglyceride levels in the two groups was statistically significant (p value was <0.05.)

Association between NAFLD and Retinopathy

Out of the six patients having retinopathy, four had fatty liver while two patients had normal ultrasound of the abdomen.

Group	Retinopathy Present	Total Patients	Prevalence
NAFLD group	4	48	8.33%
Non-NAFLD group	2	52	3.85%

Table 18. Association between NAFLD and Retinopathy

Group	Retinopathy Present	Retinopathy Absent	p value
NAFLD Group	4	44	0.4232
Non-NAFLD group	2	50	

The observation showed that the prevalence of retinopathy was high in the NAFLD group as compared to the non-NAFLD group. However, it was not statistically significant. (p value was > 0.05). This showed that the prevalence of DR was high in NAFLD group as compared to non-NAFLD group, but there was no statistically significant association of NAFLD with DR in newly diagnosed T2DM patients.

DISCUSSION

T2DM is an insidious illness with a long preclinical asymptomatic phase during which patients may be exposed to the ill-effects of asymptomatic hyperglycaemia for many years before they are diagnosed. The study was conducted to measure the prevalence of NAFLD and DR in newly diagnosed cases of T2DM. The average age of onset of T2DM in our study was 51.35 ± 6.37 yrs. whereas age group is higher (>65 years) in the developed countries.[14,15]

Of the 100 patients in our study population, 48% had fatty liver. In the study by Somalwar AM.[16] 56.6% of patients with T2DM had fatty liver whereas Targher et al in their study found the prevalence of NAFLD in T2DM to be 69.5%.[11] and by Kalra S et al[17] as 60%. Banerjee et al[18] found that a longer duration of T2DM was significantly associated with NAFLD. However, these studies included subjects irrespective of their duration of diabetes. This might be the reason for relatively low prevalence of NAFLD in the present study as only newly diagnosed cases of T2DM were included in the study.

Among the newly diagnosed T2DM patients having NAFLD, most of the patients had mild-moderate grade of NAFLD (95.8%), very few patients had severe grade NAFLD.

The mean BMI in NAFLD group was 27.24 ± 2.07 whereas mean BMI of patients without NAFLD was 25.55 ± 1.47. This difference between the two groups was statistically significant. Similar results were reported by Somalwar AM.[16] Vishwanathan et al[19] and Targher G et al.[11] This suggests that most of the patients with NAFLD were obese and had a high BMI value (>25). Further, it was noted that there was a statistically significant association between the increase in BMI and severity of NAFLD. So, BMI can be used both as a predictor of as well as a marker of severity of NAFLD.

Patients with NAFLD had a mean HbA_{1c} of 8.13% while those without NAFLD had a mean HbA_{1c} of 7.71%. The difference was statistically significant as the p value was <0.05. This was in concordance with many studies which proved that poor Glycaemic control reflected by higher HbA_{1c} is associated with more chances of developing NAFLD.

The mean triglyceride level of patients with NAFLD was 183.75 ± 52.14 mg/dL. Somalwar AM et al[16] observed the mean triglyceride level to be 177.40 ± 18.91 mg/dL, which was in accordance with the present study. Triglyceride levels of patients with mild NAFLD was 170.83 ± 43.08 mg/dL, of those with moderate NAFLD was 198.69 ± 51.86 mg/dL, whereas patients with severe NAFLD had a mean triglyceride level of 258 ± 33.94 mg/dL. Statistical association was observed with p value <0.0001 between severity of NAFLD and triglyceride levels suggesting that triglyceride levels had predictive value for NAFLD. The

findings of the present study were in accordance to the study done by Razavizade et al.[20]

Mean liver enzyme SGOT (AST) levels in patients of NAFLD group was 45.25 ± 17.13 and SGPT (ALT) was 53.23 ± 17.36 IU/L. In the study by Kalra S et al.[17] the mean SGOT levels in T2DM patients with NAFLD was 54.8 ± 36.1 IU/L and mean ALT levels was 55.6 ± 39.8 IU/L which is in accordance with the present study. Similar findings were also observed in the study done by Razavizade et al**.**[20] Somalwar AM et al[16] reported a mean SGOT level of 35.79 ± 6.27 and m SGPT level as 40.70 ± 7.06, while Viswanathan V et al.[19] found mean SGOT level to be 29.3 ± 17.9 IU/L and mean SGPT level of 37.6 ± 24.9. Both results did not correlate with the present study.

The prevalence of DR in newly diagnosed T2DM patients in this study was 6%. This was in accordance with CINDI study where prevalence of DR was reported to be 6.9% in newly diagnosed cases of T2DM.[21] Another study from South India 'CURES' reported prevalence of DR in newly diagnosed cases of T2DM to be 5.10%.[22] This was also in accordance with present study. However, the prevalence was found to be 2.8% only in SN-DREAMS III study,[23] which being quite lower did not correlate with the present study.

Studies from abroad have shown higher prevalence of DR at the time of diagnosis of T2DM. A study from Romania reported 14.37% prevalence while that from Taiwan reported 25.5%.[24-25] In United Kingdom Prospective Diabetes Study (UKPDS), the prevalence of DR in newly diagnosed cases of T2DM was found to be 35%.[24]

Of the six patients with DR, four had NAFLD and two had normal ultrasound examination. This showed a high prevalence of DR in the NAFLD group as compared to the non-NAFLD group. Vijay Viswanathan et al,[19] Somlawar AM[16] also reported higher prevalence of DR in patients with NAFLD and this was in accordance with the study.

CONCLUSION

The prevalence of NAFLD in newly diagnosed cases of T2DM was 48%. Most of the patients had mild-moderate NAFLD. BMI, SGOT, SGPT and triglycerides had a significant statistical association with the severity of NAFLD. The prevalence of DR in newly diagnosed cases of T2DM was found to be 6%. It was high in the NAFLD group as compared to the non-NAFLD group. However, there was no statistically significant association of NAFLD with DR.

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