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IN PERSONS WITH TYPE 2 DIABETES IN THE REGION OF INDIA, THE PREVALENCE OF NON-ALCOHOLIC STEATOHEPATITIS

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ABSTRACT

BACKGROUND: The inspiration for this research was drawn from the highly frequent finding of ultrasonography reports which mentioned fatty infiltration of the liver with hepatomegaly‖ in T2D patients undergoing routine investigations. The reason for embarking on this research project was to find out the prevalence of NASH, which was considered the advanced form of fatty liver, and to evaluate the nature of the factors which increased the occurrence of NASH and its complications in people with T2D. The assessment was done with questionnaires, clinical examination, laboratory tests, and VCTE by trained and experienced medical personnel following standard protocols. Earlier studies on prevalence in India have relied on ultrasonography which was inadequate for the diagnosis of NASH.

AIM: The primary aim of the clinical study was to determine the prevalence of NASH in adults with T2D living in the region of India.

MATERIAL AND METHOD: This study was designed as a prospective, cross–sectional, observational study of adults with T2D living in a region of India. It was undertaken to provide an estimate of the current prevalence of NASH in the Indian region, which included areas around the city. This study will also determine the prevalence of factors that cause higher risks and their significance as predictors of NASH in patients with T2D. The cohort of subjects was derived by enrolling patients of T2D from three centers. All the patients with T2D attending these three medical clinics were offered enrolment in this study after they were explained the purpose by a nursing assistant. Medical and social history, lifestyle, smoking, alcohol drinking, physical activities, and clinical data were obtained using standard questionnaires. From the preliminary data collected, 500 subjects were enrolled in the study.

RESULTS: A cohort of 500 adults with T2D was evaluated and it was observed that NASH was present in 30% of the cohort studied. The prevalence in women was significantly higher than the prevalence seen in men. These percentages are low compared to a general population which does not specifically include subjects with T2D because the majority of adults with T2D are overweight or obese, and lean NAFLD is far less common in this group compared to a general population. This study has found that though there is a significant association of liver transaminases with liver fibrosis, these tests lack adequate sensitivity and specificity to be considered important biomarkers for NASH in T2D.

CONCLUSION: The findings in this study strongly suggest that there is a need to develop strategies to increase awareness among physicians and increase their motivation to implement multifactorial interventions to prevent the progress of NAFLD to advanced stages of NASH and severe fibrosis, which may lead to the development of CVD complications, cirrhosis, and hepatocellular carcinoma. The burden of complications due to NASH in patients with T2D is huge because of the sheer number of patients and this will prove to be a major strain on public health resources.

KEYWORDS: Acute Myocardial Infarction, Alcoholic Liver Disease, Alanine Aminotransferase, Arterial Stiffness, Adipose Tissue Dysfunction.

INTRODUCTION:

The enormous increase in the reported prevalence of type 2 diabetes (T2D) and its complications exerts immense strain on healthcare resources globally, especially in developing countries. The burden due to diabetes mellitus and its complications is tremendously high due to the presence of 463 million people with diabetes globally, including 116

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million in China, 88 million people in South Asia, and 77 million who reside in India.[1] It is expected that by the year 2030, the prevalence of diabetes will exceed 8.6 billion worldwide, with 140 million in China and 101 million in India, the two countries with the highest burden.[1] India has an estimated population of 44 million people with undiagnosed diabetes, which constitutes 57% of the total number of Indians estimated to have diabetes.

Current guidelines do not recommend routine screening for NAFLD because long–term benefits have not been clearly defined and the costs are prohibitive. Liver function tests may be normal in a majority of patients with T2D and NASH, and hepatic scores which rely mainly on serum transaminase levels are unreliable for diagnosis.[2] According to Marcuccilli and Chochol, delay in the detection of NASH and its complications increases morbidity and mortality due to advanced fibrosis, cirrhosis, HCC, CVD, and renal disease in patients with diabetes.[3] In addition to the lack of guidelines for screening due to specific comorbidities, the delay in diagnosis of NASH is due to non–the availability of a specific and highly accurate method.[4] Determining the prevalence of NASH is important for assessing the high disease burden and complications due to liver disease in adults with T2D.

Fatty liver is defined as macroscopic steatosis in more than 5% of hepatocytes confirmed by histological examination. A higher cut–off of 5.6% is applicable for magnetic resonance spectroscopy, which corresponds to 15% hepatic steatosis by histological examination.[5] NAFLD is diagnosed only after the exclusion of liver disease by other aetiologies like alcohol–induced liver disease, drug-induced chronic liver disease, viral or autoimmune hepatitis, and cholestatic, metabolic, or genetic liver disease.[6]

The normal liver does not store fat in physiological conditions.[5] Fatty infiltration of the liver occurs in NAFLD, which is defined as confirmed steatosis in at least 5% hepatocytes in the absence of all secondary causes of chronic liver disease namely alcohol, drugs or toxins, viral infections, autoimmune disorders, cholestasis, and metabolic or genetic disorders.[7] NAFLD includes simple steatosis, steatohepatitis, fibrosis, and cirrhosis as progressive stages of hepatic disease and is classified into the nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). [8] A study from Finland extending over 21 years reported that NAFLD without metabolic syndrome is a benign condition and does not increase metabolic or cardiovascular risk, whereas NAFLD when combined with metabolic syndrome significantly increases CVD, the incidence of T2D, and left ventricular mass index.[9] Simple hepatic steatosis is not all that innocent.

The risk factors for the development of NAFLD are advancing age, ethnicity, presence of metabolic syndrome, type 2 diabetes (T2D), male gender, menopause, hypertension, high dietary fat, high carbohydrate, and especially high fructose in the diet, genetic predisposition, and obstructive sleep apnoea. Risk factors for progression to NASH are older age, diabetes, alcohol consumption, excessive smoking, and increased liver enzymes.[10][11] The currently available biomarkers and diagnostic panels cannot differentiate NASH from the various stages of NAFLD. Though combinations of tests that use cytokeratin–18 (Ck–18) have been investigated by many centers, their reproducibility is not faultless and specificity is not adequate.[12]

MATERIAL AND METHODS

This study was designed as a prospective, cross–sectional, observational study of adults with T2D living in a region of India. It was undertaken to provide an estimate of the current prevalence of NASH in the Indian region, which included areas around the city. This study will also determine the prevalence of factors that cause higher risks and their significance as predictors of NASH in patients with T2D. The cohort of subjects was derived by enrolling patients of T2D from three centers. These three centers represented a variety of patients from different socioeconomic levels. Consecutive patients who attended as outpatients in the general medical clinic formed one group. The two other centers from where the subjects were enrolled were medical clinics run by general physicians attending all patients with medical problems which included patients with T2D. Such a mixture of patients would most closely represent the general community.

The patients represented the general community of patients with diabetes, not a group with complications referred to a specialized diabetes clinic. Physician assistants trained in clinical methods collected detailed information from 1986 patients with T2D recruited consecutively for this study. Medical and social history, lifestyle, smoking, alcohol drinking, physical activities, and clinical data were obtained using standard questionnaires. From the preliminary data collected, 500 subjects were enrolled in the study. Anthropometric measurements taken included body weight, height, and waist circumference at the center of the distance from the lowest rib to the upper border of the iliac crest in the late exhalation period while standing. Blood pressure was measured on the left arm 10 minutes after the subject was seated comfortably.

An electronic monitor by OMRON was used for BP measurement. An average of three measurements taken at one–minute intervals was taken for this study.

Inclusion criteria

- ✓ Patients who are willing for the study and have given written, informed consent prior to enrolment
- ✓ Females or males, aged 30 years or more
- ✓ Established cases of type 2 diabetes
- ✓ Patients who give no history of any current or previous liver disease
- ✓ Non–alcoholic patients, identified with the AUDIT questionnaire (Limits currently applicable for Alcohol consumption are < 20 g/day in men and < 10 g/day in women)

Exclusion criteria

- ✓ Patients with other causes of chronic liver disease
- ✓ Those who give a history of taking hepatotoxic drugs: methotrexate, amiodarone, nitrofurantoin, isoniazid, ticrynafen, enalapril, valproic acid, clometacin, infliximab, methyldopa, minocycline, glucocorticoids, metoprolol, and tamoxifen.
- ✓ Those who have a history of chronic liver disease or cirrhosis with or without ascites

Elimination of Bias

- ➢ Selection bias was avoided by including consecutive patients with diabetes who came to the outpatient clinic for their routine check–up. The screening was done for all the patients enrolled in the study.
- ➢ Ascertainment bias was avoided by not recruiting a subject if there was a history of steatosis or abnormal liver tests recently for which the patient was referred to a hospital.
- ➢ Operator bias was removed by using the Fibroscan technique for the diagnosis of NASH, which is a previously validated technique for the assessment of liver fibrosis by Transient elastography.[13] Fibroscan is not operator–dependent and eliminates inter–observer variability as compared to ultrasonography.[14] However, a single, trained, certified and experienced technician assessed all the cases in this study, with no information on the cases other than the name and age of the subjects.

Liver biopsy was not a feasible option because of the risk of complications, the reluctance of patients to give consent especially when they had no history or symptoms or signs of any liver disease, and inter– and intra–observer variability in biopsy technique and reporting.

The NAFLD Fibrosis Score (NFS) has been validated by several studies and has been found to have a positive predictive value of 82%.[15] TE was performed using FibroScan® 502 Touch (Echosens, Paris, France). An M–probe was used and all tests were performed by a qualified operator who has been certified by the manufacturing company.

Statistical analysis

Microsoft Excel (Microsoft Corporation, Redmond, WA) was used for data recording and analysis for mean, median, and other routine calculations. Categorical data are expressed as numbers and percentages. Normally distributed data are reported as mean ± standard deviation and skewed distribution data are reported as the median and interquartile range (IQR). The unpaired Student‘s t–test or Mann – Whitney U test was used to compare two groups, and the one–way analysis of variance or the Kruskal– Walls H test was used for comparing multiple groups.

RESULT: -

Researchers from the Johns Hopkins University, USA studied 11,371 adults in the USA with hepatic steatosis and NASH, diagnosed only by ultrasonography and hepatic enzymes, and reported that NAFLD did not increase the death rate due to any cause or the occurrence of cirrhosis or carcinoma of the liver.[16] However, routine ultrasonography cannot diagnose fibrosis nor can liver enzymes clinch the diagnosis of NASH. Such a study based on inadequate methods of diagnosis would give erroneous results, and conclusions based on these cannot be relied upon for any useful inferences. Subsequent researchers have shown that hepatic fibrotic damage in NASH accelerates the advancement to liver failure and increases the death rate [17][18]

Table 1: Baseline characteristics of cardiometabolic conditions which have an adverse effect in T2D, classified by gender.

Subgroups of the Cohort	Men (n, 250)	Women (n, 250)
	Median ± IQR	
BMI	24.1±2.5	25.4±5.3
HbA1c	5.3±1.0	5.6±1.4
T. Chole	155±45	170.5±30.3
LDL	93±33	95.2±25.1
Triglycerides	113±80	118±62.5
HDL	31±8	40.2±13.1
S. Creatinine	0.77±0.16	0.5±0.1
SGOT	19±11	20±5
SGPT	21±18	20±10
SGGT	22±21.3	21±11
Alk. Phosphatase	92±33.5	88±44
Albumin	2.1±0.5	2.1±0.3
NFS	–0.03±1.01	0.20±1.09
PWV	5.4±1.4	5.75±1.4
LSM	3.4±1.3	3±2.35

The data from the study conducted for this thesis in Table 1 shows the baseline characteristics with median values of the factors that cause increased risks in men and women, and the median and mean in the total cohort.

Table 2: Shows the median values of the factors that cause increased risks in this study of a cohort of T2D, classified into NASH and Non–NASH groups

Subgroups of the Cohort	NASH (LSM ≥7 kPa)		Non–NASH (LSM	
	Men (n, 125)	Women (n, 125)	Men (n,125)	Women (n,125)
	Median ± IQR			
BMI	22.5±3	27±5.1	22.3±2.3	21.2±3.1
HbA1c	4.9±1.0	5.4±2.0	6.2±1.4	5.4±1.2
T. Chole	150±30	174.3±30.3	155±43	140±33
LDL	88±24.3	105±32.1	97±33	101±35
Triglycerides	121.2±75.2	147.4±66.02	116±55	105.2±62.1
HDL	20±5.4	36±12	33±08	25±12
S. Creatinine	0.8±0.3	0.7±0.2	0.85±0.3	0.7±0.2
SGOT	18±07	14±12	14±09	12±4.3
SGPT	16.2±18	17±07	19.5±11	19±06
SGGT	21.2±17	19±10.2	16±11	12±06
Alk. Phosphatase	94.3±22	103±44.4	90±22.2	94.2±39
Albumin	2.3±0.4	2.4±0.4	2.2±0.3	2.1±0.3
NFS	0.5±0.54	-1.2±0.5	– 0.63±1.51	–0.22±1.3
PWV	4.3±1.3	4.3±1.4	5.2±1.4	5.2±0.3

The liver enzymes are higher in men compared to women, while lipids are higher in women compared to men. These differences may be due to the presence of T2D in the cohort studied.

DISCUSSION

The present research is the first one in India in which a large cohort has been studied with the validated method of Transient Elastography with Fibro Scan for the diagnosis of NASH and advanced fibrosis in patients with T2D. The cut-off value of ≥ 7 kPa was used for identifying subjects with NASH in this study. The result for the extent of the presence of NASH in the study conducted for this thesis shows a much higher proportion compared to the study by Williams et al. who have reported the extent of the presence of NASH in T2D subjects as 22.2%, which was three times higher compared to those without T2D.[19] A Scandinavian study has reported that NASH was present in 17.6% of patients with diabetes.[20] However, my results are similar to what was reported in a small study by previous researchers from Australia who used TE and diagnosed NAFLD and significant fibrosis in 35% of 74 patients with T2D, and subsequent liver biopsy in their cohort confirmed NASH in 92% of those cases. [21]

In a US study of 435 subjects with diabetes and NAFLD, the extent to which NASH was present was reported as 69.2% and advanced fibrosis was present in 41%. [22] In their cohort, the mean age of the patients was 52.5 years (SD±10.3 years), and the mean BMI was 35.8 kg/m2 (SD±6.8 kg/m2).[22] In contrast, data from the study conducted for this thesis shows that in the total cohort, the median age and IQR were 55 ±16 years in both women and men. The median BMI in the total cohort in the study conducted for this thesis was 26.9 kg/m2 ±IQR 6.3. In women, the mean BMI was 28.9±IQR 7.5, while in men it was 26.2±IQR 4.9. The higher prevalence of obesity in the US cohort could explain the increased occurrence of NASH in patients with diabetes and NAFLD in the USA. An earlier study conducted by us on 588 subjects with T2D, presented at the ADA annual conference in 2019 in San Francisco, USA showed the presence of NASH in 30% of the total cohort, with 34.7% in women and 26.3% in men.[23] The addition of further subjects to this cohort has shown the same rate of prevalence of NASH in the geographical region studied. An earlier pilot study conducted by me on 246 patients of T2D had also shown a similar prevalence in this region (unpublished data). The absence of any change in the percentage also confirms that the sample size is more than adequate for this study on the prevalence of NASH in T2D

A high prevalence of NAFLD in Asians has been reported in non–obese individuals, varying from 11% to 31.7%, which has been named as the _Asian Paradox‘. [24][25] The increased risk of NAFLD, possibly due to high insulin resistance (IR) in lean individuals with normal BMI, has been attributed to the ―metabolically obese‖ factor in different ethnic communities.[26] Ozturk et al (2016) have shown that the arterial wall produces pentraxin 3, which is a biomarker of inflammation, and this is raised in NASH but not in NAFLD patients without fibrosis nor in healthy subjects, and this relationship is not related to the presence of a combination of hypertension, abdominal obesity, hyperglycemia and dyslipidemia its components.[27]

Petit et al (2009) have stated that the link between NAFLD and atherosclerosis in patients with T2D is not established.[28] They studied subjects with type 2 diabetes by evaluating the hepatic fat content using a 1H–magnetic resistance spectroscopy. Hepatic steatosis was confirmed when the triglyceride content in the liver was greater than 5.5%.[29] The method for calculation of fat content in the liver has been described by Guiu et al,2009. [30]

Guo et al (2017) observed that NAFLD was linked with carotid and lower limb atherosclerotic plaques independent of conventional CVD conditions which increase the risk and independent of the individual factors in the combination of hypertension, abdominal obesity, hyperglycemia and dyslipidemia in Chinese patients with T2D.[31]

Wild et al (2018) have observed a retrospective cohort study on 134,368 people with T2D, 1,452 of whom had NAFLD.[32] Their mean follows–up was 4.3 years for CVD and 4.7 years for mortality. The Hazard ratio and 95% Confidence Intervals for complications for T2D patients with NAFLD were CVD 1.70 (1.52– 1.90), hepatocellular carcinoma 19.12 (11.71–31.2), nonhepatocellular carcinoma 1.28 (1.12–1.47), and for all–cause mortality 1.60 (1.40–1.83). They also observed that there was an increased incidence of CVD if there was a previous history of hospitalization.

Kim et al (1999) have observed that hypoalbuminemia correlated with CVD and they hypothesized a _dependent cause–effect relationship and an _effect–effect relationship‘, which may be through inflammation.[33] Hypoalbuminemia increased the plasma levels of lipoprotein and fibrinogen and increased the aggregation of platelets and the viscosity of blood.[33] However, Djousse et al (2003) have observed that low albumin levels were not linked with CIMT.[34] In contrast, a study from S. Korea observed a relationship between higher serum albumin with increased risk for the combination of hypertension, abdominal obesity, hyperglycemia, and dyslipidemia.[35]

CONCLUSION:

The findings in this study strongly suggest that there is a need to develop strategies to increase awareness among physicians and increase their motivation to implement multifactorial interventions to prevent the progress of NAFLD to advanced stages of NASH and severe fibrosis, which may lead to the development of CVD complications, cirrhosis, and hepatocellular carcinoma. The burden of complications due to NASH in patients with T2D is huge because of the sheer number of patients and this will prove to be a major strain on public health resources.

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