The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/2020.27.08.4617

ORIGINAL PROF-0-4617

FREQUENCY OF PRE-DIABETES, DIABETES MELLITUS IN NON-ALCOHOLIC FATTY LIVER DISEASE.

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Article received on:
05/03/2020
Accepted for publication:
06/06/2020

ABSTRACT… Objectives: To determine the prevalence of diabetes mellitus and pre-diabetes among patients with NAFLD having BMI ≥ 25 kg/m^{2}and compare it with the control group with non-fatty liver with same BMI. **Study Design:** Prospective, Analytical and Cross-sectional study. **Setting:** Department of Medicine, Civil Hospital Karachi. **Period:** January 2015 to October 2016. **Material & Methods:** The study was conducted among two groups of patients, one with non-alcoholic fatty liver disease (NAFLD), having BMI of ≥25kg/m^{2}and they were compared with a control group having BMI≥25kg/m^2 but without fatty liver on ultrasound. **Result:** Out of 201 NAFLD participants, 82.08% had pre-diabetes and diabetes mellitus, while 82.51% of participants from non-NAFLD (n=101) had pre-diabetes or diabetes mellitus. Insulin resistance was more common among non-NAFLD group than NAFLD group. Most of the metabolic parameter analysed in the study among two groups having slight difference, and they were statistically significant. **Conclusion:** Pre-diabetes and diabetes mellitus is a frequently reported problem among NAFLD and overweight/obese patients. Insulin resistance was found to be a significant predictor of diabetes mellitus.

Key word: Diabetes Mellitus, Insulin Resistance, NAFLD, Obesity, Pre-Diabetes.

Article Citation: Jabeen R, Mobin A, Mehmood K, Ali ST. Frequency of pre-diabetes, diabetes mellitus in non-alcoholic fatty liver disease. Professional Med J 2020; 27(8):1703-1709. **DOI:** 10.29309/TPMJ/2020.27.08.4617

INTRODUCTION

Diabetes Mellitus is a chronic health problem in every part of the world, including all age groups. At least 382million people ageing 40-59 years are affected by diabetes mellitus world over and going to be doubled by 2035.[1] Estimated 1.5 million people died every year because of its complications.[2] In Pakistan the prevalence of diabetes mellitus is 11.77%, and Pakistan is at 6th number among 10 countries with highest prevalence of diabetes mellitus.[3]

Non-alcoholic fatty liver disease (NAFLD) is a clinic-histopathological entity with histological features that resemble alcohol induced liver injury but can occurs in patients with little or no alcohol consumption. The pathogenesis of NAFLD has not fully elucidated. It encompasses a histological spectrum that ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis to hepatic steatotsis with a necro inflammatory component that may or may not have associated fibrosis. The latter condition is termed as non-alcoholic steatohepatitis (NASH)[4], which is now recognized as a leading cause of cirrhosis of liver.[5] NAFLD is seen worldwide and is the most common liver disease in Western countries. The major risk factors for NAFLD includes central obesity, type 2 diabetes, dyslipidaemia and metabolic syndrome.[6] In USA the prevalence of NAFLD is 10-46%, and of NASH is 3-5%, and they are biopsy proven[7] which is a gold standard test for the diagnosis of fatty liver. Although ultrasound is more commonly used, because of increased risk and high expenditure of liver biopsy, especially in developing countries.[8] Worldwide, the prevalence of NAFLD is 6-35%. In one study, the prevalence of NAFLD among Asia-Pacific region ranges from 5-30%.[9] Most patients of NAFLD are in their 40-50s, occurring equally in males and female.[10] Patients with NAFLD and particularly of NASH, often have one or more component of metabolic syndrome, including obesity, systemic hypertension, dyslipidaemia,

insulin resistance or overt diabetes.[11] There are also data suggesting NAFLD is associated with post cholecystectomy[12], and those who never had surgery for gallstones do not develop fatty liver. Other conditions that may be associated with NAFLD are polycystic ovary syndrome, hypothyroidism, Obstructive sleep apnoea, hypopituitarism and hypogonadism.[13] Most patients with NAFLD remain asymptomatic or sometimes may present with fatigue, malaise, vague right hypochondrial pain or hepatomegaly. There may be elevated liver enzymes including alanine aminotransferase, alanine aminoaspartate, alkaline phosphatase and gamma glutamyltransferase or hepatic steatosis on ultrasound.[14] Serum ferritin greater than 1.5 times normal may be associated with higher non-alcoholic fatty liver disease activity score and with advanced hepatic fibrosis.[15]

Insulin resistance has a key role in the development of hepatic steatosis, and steatohepatitis.[16] Obesity and type 2 diabetes are frequently seen in patients with NAFLD. Insulin resistance is also seen in patients of NASH, who are not obese neither have impaired glucose tolerance.[16] The reported prevalence of impaired glucose tolerance among obese children and adolescent ranges from 21-25%, and the prevalence of type 2 diabetes mellitus is around 4%.[17] Fasting plasma glucose between 100-125 mg/dl, or HBA1C between 5.7 & 6.4% suggests impaired glucose tolerance and should be further evaluated by an oral glucose tolerance.[18]

The aim of this study is to determine the frequency of pre-diabetes, diabetes mellitus in overweight or obese patients with or without NAFLD, and co-relate it with insulin resistance. By early detection of pre-diabetes or diabetes mellitus will help to reduce not only the complications related to it but also the cost affecting the community and the patient itself.

MATERIAL & METHODS

This prospective, analytical, cross-sectional study was conducted in a tertiary care Hospital of Karachi, during the period of January 2015 to October 2016. Total enrolled patients were segregated into two groups, having same age group between20-50 years. First group included had fatty liver on ultrasound having BMI ≥25kg/m^2, and the control group had BMI ≥25kg/m^2 without fatty liver on ultrasound. Patients already having diabetes mellitus, hepatitis B, hepatitis C and alcoholism were excluded from the study.

Metabolic Parameters

All patients were subjected to have fasting sugar, HBA1C, lipid profile, fasting insulin, liver function test and ultrasound liver. The ultrasound features of fatty liver include a hyperechoic liver where the echo-texture of the liver is brighter than the kidney and blurring of vascular markings.[19] Hepatitis B and C were done in all patients. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated to evaluate insulin resistance. It is categorized as normal insulin resistance when HOMA score is <3, moderate IR: between 3 and 5, and severe IR when it is >5. A standard OGTT with 75 gm glucose, was carried out in all patients. Fasting plasma glucose and impaired glucose tolerance are defined as a fasting glucose ≥ 100mg/dl but <126 mg/dl, and a 2 -hour post load glucose on the OGTT of ≥ 140 mg/dl but <200 mg/dl respectively. Participants were labelled as diabetic and pre-diabetics according to ADA criteria of HbA1C, one labelled as diabetic with HbA1C of ≥6.5% and pre-diabetics when HbA1C is between 5.7-6.4%."

Anthropometric Indices

Weight was measured in kg using a calculated digital scale, while height was measured using a stadiometer. Waist circumference (WC) was measured by palpating the right iliac crest, crossing the mid axillary line and placing the measure around the trunk's body at minimal respiration on the standing position. Hip circumference (HC) was assessed above the hips at maximum extension of the buttocks. The waist hip ratio (WHR) was the ratio between waist and hip curve. In relation to WHR, abdominal obesity is defined as WHR > 0.90 for males and above 0.85 for females. BMI was calculated as the weight in kg divided by height in meter squared. For Asian population BMI criteria is different, people are labelled as pre-obese if falls between 25 to 29.9

kg/m^2, and obese if BMI is greater than 30kg/m^2."

RESULT

Out of 302, participants enrolled in the study, NAFLD was present in 201 patients having BMI ≥25kg/m^2 and they were compared with 101, non-fatty liver patients with same BMI. Out of 302 participants, 187 (61.9%) were female and the maximum number of patients were from the age group 31-40 years (41.7%). The patient's demographic characteristics in both groups are summarized in (Table-I).

Regarding metabolic profile fasting glucose and 2 hours glucose were significantly higher in more than 50% of patients, in both study groups. Triglycerides and cholesterol were also raised in most of the patients in both study groups as shown in Table-II. Pre-diabetes was found in 45.27% and type 2 DM in 36.8% of participants having NAFLD, while in non-NAFLD group type 2 diabetes was more common than pre-diabetes (Figure-1). Insulin resistance is most significant in participants with increased BMI but almost having same percentage in both study groups (Figure-2).

Variable	Properties	Group with NAFLD	Frequency%	Group without NAFLD	Frequency%
Sex	Male	75	24.83%	40	13.24%
	Female	126	41.72%	61	20.12%
Age	20-30 years	43	14.24%	32	10.59%
	31-40 years	87	28.80%	37	12.25%
	41-50 years	72	23.84%	31	10.26%
BMI (kg/m^2)	25-29	70	34.8%	15	14.8%
	30-34	68	33.8%	30	29.7%
	>35	63	31.34%	56	55.44%
	>35	51	25.3%	49	48.51%
WHR	Low	59	19.53%	26	8.60%
	Moderate	46	15.23%	12	3.97%
	High	96	31.78%	63	20.86%

Table-I. Frequency of demographic and anthropometric profile among two groups.

	NAFLD	Without NAFLD	P-Value
0hr sugar (mg/dl)	106.4±24.02	120.2±40.79	.000
2hr sugar (mg/dl)	157.9±91.54	179.5±79.2	.000
HbA1C %	6.35±0.93	6.67±1.31	.017
Fasting insulin (uU/ml)	17.13±9.95	14.96±8.34	.061
HOMA- IR	4.56±3.04	4.40±3.11	.677
WHR	0.89±0.06	1.71±8.06	.041
BMI (kg/m^2)	32.28±6.12	35.48±5.56	.000
ALT IU	38.56±21.74	43.27±23.4	.085
ALP IU	105.3=43.6	132.3=60.2	.000
Cholesterol(mg/dl)	205.0=92.06	220.4-66.26	.008
Triglyceride (mg/dl)	168.5=64.59	172.0=57.8	.649
HDL (mg/dl)	34.87±10.04	31.94±9.65	.016
LDL (mg/dl)	122.0=72.75	126.0=48.96	.112

Table-II. Frequency of anthropometric & metabolic profile among both groups.

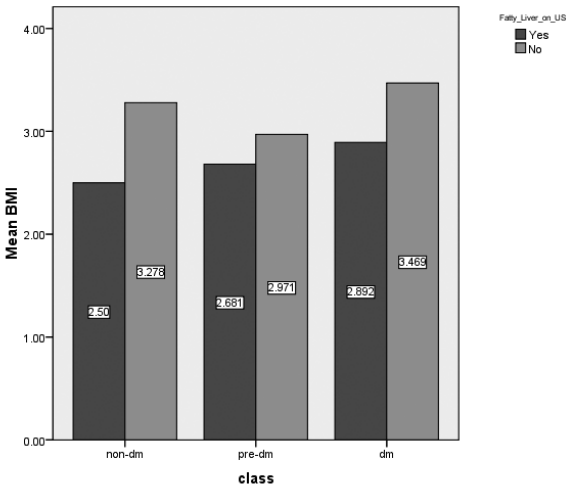

Figure-1. Classification of diabetes mellitus among both groups in relation to BMI.

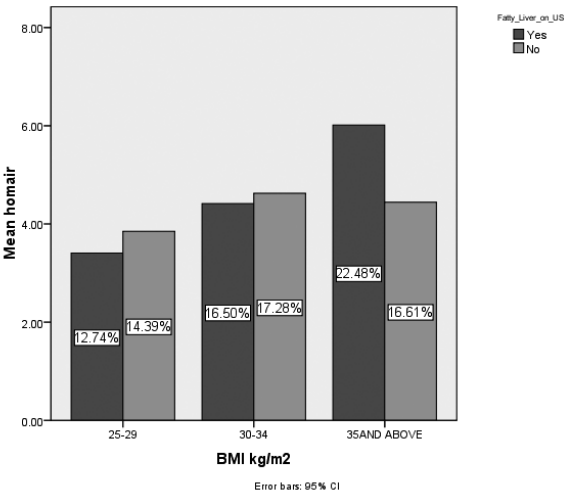

Figure-2. Co-relation of BMI with homa-ir in both groups.

DISCUSSION

Type 2 Diabetes Mellitus, is characterized by hyperglycaemia, insulin resistance, and relative impairment in insulin secretion. Prediction and prevention of type 2 DM, in general population is limited, but there are certain population who can be targeted including individuals who have increased fasting glucose, impaired glucose tolerance, obesity, immediate family members with type 2 Diabetes Mellitus.[20,21]

NAFLD currently is recognized as an important health problem, it encompasses a variety of liver pathologies including steatosis, non-alcoholic steatohepatitis, fibrosis, cirrhosis and even cancer.[22] NAFLD is described by Ludwig, three decades ago and defined as fatty liver having liver fat>5-10% of liver weight, and it must not be due to alcohol or other cause of steatosis.[23] NAFLD is the most common cause of chronic liver disease in United States and is becoming common in South East Asia as well. The prevalence of NAFLD in South East Asia and South Asia is ranges from 5-30%, and a Hospital based study done in Pakistan showing frequency of 14%.[24] In India, the prevalence of fatty liver among healthy individual is 5-28%. Indians having propensity of visceral fat accumulation.[25] Although the risk for developing DM, is commonly seen in patients with increased fasting glucose, impaired glucose tolerance and increased HbA1C, but it is more commonly seen among patients with HbA1C between 5.7-6.4% (39-46 mmol/ml). The other additional feature is obesity i.e. BMI ≥25kg/m^{2}and the family history.[26] In our study the fasting insulin and Homa-IR was slightly higher in NAFLD group with a p value of 0.061. All other metabolic profile is statistically significant in both groups, except triglycerides and ALT .Level of HbA1C is also raised in non-NAFLD group having a diabetic range which is against one study done in Iran in 2016.[27] Studies have shown that prevalence of NAFLD increases with age which is also seen in our study.[28,29] The same relationship has been seen with obesity, most of the participants included in our study with NAFLD had increased BMI ≥ 25kg/m^2. Its association has been seen in many studies, in Zelber-Sagi et.al, study, the mean BMI was 29.6+ 3.8, which is quiet co relating with our study.[30,31]

The diagnosis of NAFLD, is made on abdominal imaging, but many patients seek medical attention due to raised liver enzymes along with fatigue and upper abdominal pain.[32] There is a prevalence of deranged liver enzymes in 8% of population in 3rd National Health and Nutrition Examination. Survey done in North America, most of these deranged liver enzymes is associated with NAFLD.[33] These liver enzymes are typically normal or elevated by <5 times of upper limit of normal.[34]

The liver enzymes including alanine aminotransferase, gamma glutamyl transferase and alkaline phosphatase were increased

in 25.49%, 25.1% and 8.2% respectively, is contradicting than the earlier published studies in which there is much significantly raised in NAFLD and or obese patients.[35,36] Obesity is a state of excess adipose tissue, and is a prevalence is increasing Worldwide since 1980. The prevalence of obesity in Eastern Asia and Southern Asia is quiet low as compared to United States.[37,38] Asia pacific society has incorporated anthropometric scale as a base of obesity in Asian population. A small increase in weight of 2-3 kg may lead to development of NAFLD, but more importantly it may present even with normal weight.[39] Among Asian countries the highest obesity rate is seen in Thailand and Malaysia, while lowest is seen among Bangladesh, Vietnam and India.[40] Among Asian countries rate of obesity is twice in females than that of males[41], which is also seen in the current study with much higher numbers of female patients in the study. Obesity is associated with adverse outcome, weight loss may reduce many illnesses including diabetes mellitus, hypertension, dyslipidaemia, osteoarthritis and sleep apnoea syndrome and all these are associated with metabolic syndrome and NAFLD.[32]

CONCLUSION

Non-communicable diseases, including diabetes mellitus, hypertension, acute coronary syndrome and cancers are the major cause of deaths world over. In Pakistan, non-communicable diseases are the leading cause accounting 50% of total deaths in Pakistan. Diabetes ranked 4th among all non-communicable diseases in Pakistan. It is now clear that NAFLD and insulin resistance have a close relationship, and insulin resistance is directly linked with hypertension, diabetes mellitus and atherosclerosis. These are the conditions that have much significant mortality and morbidity.

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