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PREVALENCE OF NASH IN NAFLD PATIENTS WITH PRE-DIABETES AND DIABETES MELLITUS

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ABSTRACT

Background: Prevalence of pre diabetes and diabetes is increasing with the increasing number of patients with NAFLD or NASH. Previous studies have suggested pathological linking of diabetes mellitus type 2 with NAFLD. Impairment of insulin metabolism, either insulin resistance or hyperinsulinemia with oxidative stress and inflammation contribute to development of diabetes and NAFLD. **Material & Methods:** The present single Centre observational study was conducted at Mahatma Gandhi Medical College and Hospital, Jaipur. The study was conducted in Department of Biochemistry in association with Department of Gastrologer & Endocrinology. The study was conducted in duration of one year, after seeking approval from the Institutional Ethics Committee. **Results:** Total 200 patients were enrolled for the study. The mean age of subjects of both groups was comparable. All indices of diabetic profile namely blood sugar fasting, blood sugar postprandial, HbA1c, insulin and HOMA-IR were significantly significant in the diabetic subject as compared to pre Diabetics group. The prevalence of NASH is in Association with the progression from pre diabetic to diabetic conditions positively affect the occurrence of NASH and it was found statistically significant. However glycemic index measured by HbA1c did not have a significant impact on the occurrence of NASH in enrolled NAFLD patients. **Conclusion:** The diabetes patients are at high risk to develop NAFLD or worse condition. Early diagnosis of NAFLD helps patients to improve their condition with NAFLD by daily exercises and with Lifestyle changes and the prognosis would be better.

Key words: NAFLD, Diabetes, Pre-diabetes, NASH.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been considered a benign condition related to obesity, insulin resistance and with metabolic syndrome **(1)**. Metabolic disorders is a group of dysfunction involving glycemic metabolism and defect in insulin production and utilization and type 1 Diabetes mellitus (autoimmune destruction of Beta cell pancreas with complete deficiency of insulin) and type 2 Diabetes mellitus (where utilization of insulin decreases). Patients with metabolic disorders are at high risk of developing vascular degenerations and related complications **(2)**.

Prevalence of pre diabetes and diabetes is increasing with the increasing number of patients with NAFLD or NASH. Previous studies have suggested pathological linking of diabetes mellitus type 2 with NAFLD **(3)**. Impairment of insulin metabolism, either insulin resistance or hyperinsulinemia, disorders of lipid metabolism (Metabolism of Cholesterol, Lipoproteins and Triglycerides), with oxidative stress and inflammation contribute to development of diabetes and NAFLD. Not only life style but genetic and environmental factors also affect the progression of disease **(4)**.

NAFLD is increasing worldwide as well as in India with the prevalence about 9% to 32% in general population in India **(5)**. Prevalence is affected by occurrence of pre diabetes, diabetes and obesity, as NAFLD increases with the increase in number of patients with above mentioned disorders **(6)**. Hence, we conducted present study to evaluate the prevalence of NASH in NAFLD patients with pre-diabetes and diabetes mellitus.

MATERIALS & METHODS

The present single Centre observational study was conducted at Mahatma Gandhi Medical College and Hospital, Jaipur. The study was conducted in Department of Biochemistry in association with Department of Gastrologer & Endocrinology. The study was conducted in duration of one year, after seeking approval from the Institutional Ethics Committee. All protocols of ethical conduct including written and informed consents of the patients enrolled for the study was strictly complied. Confirmed patients of NAFLD by ultra-sonography (USG) who were visiting outpatient department of our hospital were enrolled in our study. Calculated Sample size of study was 200 and patients were equally enrolled in prediabetic and diabetic group. Detailed socio-demographic data were taken and recorded along with general physical and clinical examination. Inclusion criteria for the patients includes adults i.e. > 18-60 years of age and patients who had elevated serum ALT & AST > 2 to reference values. Patient who were alcoholic, pregnant and lactating mothers, patient with other forms of chronic liver disease such as viral or autoimmune hepatitis, medication induced liver disease, patients who had bariatric surgery, any kind of active or recent malignancy, patients on medication associated with fatty liver disease were excluded from the study. The patients selected on the basis of above defined criteria was further subjected to investigations; Aspartate transaminase (AST), Alanine transaminase (ALT) by Kinetic with pyridoxal 5 phosphate, Serum Lipid Profile, Cholesterol by Enzymatic (CHO-POD) method, Triglycerides (TG) by Enzymatic (GPO/POD) method, High Density Lipids (HDL-Chol) by Phosphotungstic Acid/MgCl2-Enzymatic method, Low Density Lipids (LDL) and Very Low Density Lipids (VLDL) shall be calculated by Friedewald formula i.e. VLDL = TG/5 and LDL= Cholesterol – (HDL+VLDL), Insulin by CMIA, Homeostatic model assessment- Insulin resistance (HOMA-IR), Viral Markers- HbsAg, Anti HCV and HIV. The results thus obtained shall be subjected to statistical analysis. The data were analyzed by using software's MS Excel 2010, Epi Info v7 and SPSS v22.

RESULTS

Total 200 patients were enrolled for the study. All the biomarkers estimated in the Enrolled patients were presented as mean and SD For the pre diabetic and diabetic groups. All the analytes were compared by applying student t-test. The mean age of subjects of both groups was comparable. For the pre diabetic group mean age was 47.24±10.27 years and for the diabetic group mean age was 46.36±8.36 years. As expected all indices of diabetic profile namely blood sugar fasting, blood sugar postprandial, HbA1c, insulin and HOMA-IR were significantly higher (p value < 0.001) in the diabetic subject as compared to pre Diabetics group. (Table 1)

Table 1: Diabetic profile in pre-diabetic and diabetic patients of NAFLD

Parameters	Mean ± SD		t-value	P value
	Pre DM	DM		
Age (years)	47.24±10.27	46.36±8.36	0.665	0.507
Glucose Fasting (mg/dl)	110.22±7.05	171.87±57.61	-10.622	0
Glucose PP (mg/dl)	133.01±17.15	249.02±66.09	-16.991	0
HbA1c (%)	6.04±0.20	8.76±1.99	-13.6	0
Insulin (uIU/ml)	5.76 ±6.45	18.25±6.25	-13.907	0
HOMA-IR (score)	1.55±1.64	7.81±4.06	-14.296	0

In the present study the the prevalence of NASH is in Association with the progression from pre diabetic to diabetic conditions positively affect the occurrence of NASH and it was found statistically highly significant by applying Chi square test (x2 = 17.383; P=0.000). (Table 2)

In the present study, however glycemic index measured by HbA1c did not have a significant impact on the occurrence of NASH in enrolled NAFLD patients by applying Chi square test (x2 = 0.005; P > 0.05). (Table 3)

Table 2: Prevalence of NASH in NAFLD patients with pre-diabetes and diabetes mellitus

Groups	Sub-groups		Chi-square	P-Value
	Pre DM No. (%)	DM No. (%)		
NASH	10 (26)	28 (74)	17.383	0.000
No NASH	90 (56)	72 (44)		

Table 3: Prevalence of NASH in NAFLD patients with HbA1c

Groups	Sub-groups		Chi-square	P-Value
	HbA1c <8.0 No. (%)	HbA1c >8.0 No. (%)		
NASH	28 (74)	10 (26)	0.005	NS
No NASH	122 (75)	40 (25)		

DISCUSSION

NAFLD is commonly associated with insulin resistance and hence with other co morbid conditions like obesity type 2 Diabetes mellitus **(7)**. The present study was planned to assess the role of different non invasive biomarkers in diagnosis and treatment of NASH in Pre diabetic and diabetic patients. In the pre diabetic group the male female ratio was74/26, while it was 65/35 in the diabetic group. Several researchers have reported the prevalence of NASH in patient with NAFLD. In the present study among the diabetic subjects 28% patients presented with NASH while among the pre diabetic subjects the prevalence of NASH was only 10%. In a review by Yki-Järvinen H et, 2010 was studied prevalence of NAFLD and NASH in Japan. It was reported that the prevalence of NASH in Diabetic patient may be as high as 30 to 40% **(8)**. previous studies have also observed that the diabetes is a risk factor for development of NAFLD and further its progress and to advanced liver disease including NASH **(9)**.

In the present study the the prevalence of NASH is in Association with the progression from pre diabetic to diabetic conditions positively affect the occurrence of NASH and it was found statistically highly significant by applying Chi square test (x2 = 17.383; P=0.000). In the present study, however glycemic index measured by HbA1c did not have a significant impact on the occurrence of NASH in enrolled NAFLD patients by applying Chi square test (x2 = 0.005; P > 0.05). Recent studies by Portillo P et al., 2014 (10) Cusi K. et al., 2012 **(11)** and Wong VW et al., 2012 **(12)** have established that plasma Glucose

level may lead to toxicity thereby activating the apoptosis pathway and hence worsened NASH. Observational studies by Angulo P et al., 2002 **(13)** & Clark JM et al., 2003 have reported increase presence of metabolic syndrome and insulin resistance among, patients of NAFLD with NASH **(14)**. Previous studies by Fabbrini K et al 2009 (15) and Sanyal AJ et al., 2001 have proposed insulin resistance to be a characteristic feature of NAFLD **(16)**.

Insulin resistance is Manifested as decreased insulin sensitivity in the muscle, liver and adipose tissue. In such condition, adipose tissue release more amount of FFA due to its resistance towards anti lipolytic effect of insulin. As a result of increased lipolysis and increased fat intake, the hepatic triglyceride synthesis is enhanced **(17)**. Machedo MV et al., 2012 have explained the pathogenicity of NASH with increased insulin resistance, FFA levels are elevated specially under post prandial conditions. These excess FFA are taken up by different organs, thereby saturating their oxidative capacity **(18)**.

This fat is chiefly accumulated as ectopic fat in the inter mayo cellular and hepatic tissue due to accumulation of ectopic fat, there is increased inflammation and reactive oxygen species. Under such condition's patient with NAFLD develops the NASH and cirrhotic changes. In simpler words, it may be suggested that in patients with type 2 Diabetes mellitus risk of NASH increases due to increased life policies and hence axis free fatty acids. this excess free fatty acid accumulates in various tissues including liver in patients with NAFLD, increased fat accumulation in hepatic tissue leads to increased inflammation due to formation of ROS. These changes increase the risk of progressive cirrhosis and NASH in patient with CLD **(19)**.

CONCLUSION

We concluded from the present study that the diabetes patients are at high risk to develop NAFLD or worse condition. Diabetes make things even worse to develop NAFLD with drastically elevated liver enzymes and Have poor prognosis. Early diagnosis of NAFLD helps patients to improve their condition with NAFLD by daily exercises and with Lifestyle changes and the prognosis would be better.

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