Evaluation of Homeostatic Model Assessment of Insulin Resistance amongst the Nonalcoholic Fatty Liver Disease Study Population

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Abstract

Background: NAFLD has been recognized as a hepatic manifestation of Metabolic Syndrome (MetS) linked with Insulin Resistance (IR) and is currently considered as the hepatic component of the Metabolic Syndrome (MetS). NAFLD is strongly associated with IR and is mostly silent which is often discovered incidentally through elevated hepatic enzyme levels. The purpose of this study is to Evaluate IR amongst the Nonalcoholic Fatty Liver Disease (NAFLD) study population in CMCH.

Materials and methods: A prospective hospital based cross sectional study was carried out in the Department of Biochemistry, Institute of Nuclear Medicine and Allied Sciences (INMAS) and Chittagong Medical College Hospital (CMCH). One hundred and fifty (150) subjects aging between 18-60 years were included in this study by non-probability consecutive sampling method. IR was evaluated by HOMA-IR.

Results: It was found that insulin resistance was more among the cases than controls. Association between NAFLD and HOMA-IR status among the study population showed odds ratio 15.23 which was statistically significant, p = < 0.001.

Conclusion: The findings of the current study suggest that there is insulin resistance in NAFLD

Key words: Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); Nonalcoholic Fatty Liver Disease (NAFLD).

Introduction

In 1980, Ludwig et al published the first systematic description of what was then an "unnamed and poorly understood" condition.[1] On liver biopsy, findings resembled those of alcoholic hepatitis, but because the patients did not have a history of heavy drinking, the condition was named "nonalcoholic steatohepatitis". Nonalcoholic steatohepatitis is now believed to be part of a spectrum of disorders that comprises NAFLD[2]. i.e. Simple steatosis (Fat accumulation within liver cells) Steatosis with nonspecific inflammation; Steatohepatitis (Fat accumulation and liver cell injury) Cirrhosis (Fibrosis, scarring and nodule formation) and Hepatocellular carcinoma.

Non-Alcoholic Fatty Liver Disease (NAFLD) comprises two-thirds of all the cryptogenic causes of chronic liver diseaseas demonstrated by Hanley et al.[3] NAFLD is also strongly associated with obesity but body fat distribution appears to play a more important role in the pathogenesis of NAFLD. There is a growing concern regarding NAFLD due to its high prevalence in the general population and its potential for progression to cirrhosis, terminal liver failure and hepatocellular carcinoma. Insulin resistance plays a fundamental role in the pathogenesis of Non-alcoholic fatty liver disease. Insulin resistance may be defined as a condition in which (a) higher than normal insulin concentrations are needed to achieve normal metabolic responses or (b) normal insulin concentrations fail to achieve a normal metabolic response.[4] The homeostasis model assessment of insulin resistance (HOMA-IR) method, as demonstrated by Marchesini et al, showed that insulin resistance was the laboratory finding most closely associated with the presence of NAFLD in a large series of patients, irrespective of BMI, fat distribution, or glucose intolerance.[5,6] Thus insulin (IR) resistance and hyperinsulinemia are the two of major factors in the pathogenesis of NAFLD.[7] IR was evaluated according to Homeostatic Model Assessment (HOMA) formula. It is calculated as fasting serum insulin (μIU/ mL) multiplied by fasting serum glucose (mmol/L), divided by 22.5 i.e. HOMA-IR = [(FBS mmol/L) X (FPI μIu/L)] ÷ 22.5.[6] The degree of insulin resistance is positively associated with the progression of intrahepatic fibrosis, whereas a decrease in insulin resistance with weight control, exercise or medication produced improvements in NAFLD.[8]

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Generally, absence of alcohol abuse or consumption of alcohol of < 20 g/day for prolonged periods, and negative serological tests for hepatitis B and C should raise the suspicion of NAFLD.[9] Before diagnostic tests for hepatitis C were available, cases of NAFLD were diagnosed wrongly as non-A and non-B hepatitis. Now after such tests for hepatitis C and E are available, NAFLD is more accurately defined. Initially it was thought to be a mild disease with little clinical significance, but at present NAFLD is recognized as a major cause of cryptogenic cirrhosis of liver.[9]

Previous results have shown that NAFLD is associated with insulin resistance and the Metabolic Syndrome (MetS).[10] In large population studies, nearly all of the NAFLD patients were found to be insulin resistant according to the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).[11] These preliminary observations have subsequently been confirmed by more direct methods for the measurement of insulin resistance like the glucose clamp technique. Employing the glucose clamp technique, Marchesini et al demonstrated a reduction in insulin-mediated glucose disposal in NAFLD.[12,13]

Hence forth, as insulin resistance was significantly related to liver fat content independently of BMI, subcutaneous fat volume and intra-abdominal fat volume assessed by Magnetic Resonance Imaging (MRI) the authors concluded that hepatic steatosis rather than adipose tissue triglyceride content can be a major determinant of insulin resistance in humans.[11] Consequently, NAFLD is now considered as the hepatic expression of the metabolic syndrome accounting for the risk of advanced liver disease.[14] Several studies have provided detailed information on the relationship between histological and clinical ndings in patients with NAFLD, demonstrating that, the higher the number of components of metabolic syndrome, the higher the risk of brosis and advanced disease.[14]

In non-obese, non-diabetic patients with NAFLD, insulin resistance is marked. Adipose tissue insulin resistance and endocrine over activity, especially in ectopic depots, may be salient features of the metabolic profile for NAFLD.[11]

Furthermore, previous study have shown that biopsy-proven NAFLD patients had marked insulin resistance which involves the hepatic tissues, adipose tissues, skeletal muscle tissues and other multiple intracellular pathways of substrate (Glucose and lipids) disposition.[11] Whether hepatic steatosis is a consequence of peripheral insulin resistance or causes insulin resistance remains unclear, but the results of previous studies suggest that excess free fatty acids especially NEFA (Non essential fatty acid) flux due to peripheral insulin resistance may contribute to hepatic steatosis.[15]

Thus considering the above information gathered and based on the research works demonstrated by different relevant authors, this study was aimed to investigate the potential relation of insulin resistance in Non-alcoholic fatty liver disease in the present context of Bangladeshi population. As a supplementary analysis, the effects of hyperinsulinemia and insulin resistance in Non-Alcoholic Fatty Liver Disease (NAFLD) patients were also evaluated. The aim of this study is to evaluate the insulin resistance in NAFLD patient.

Materials and methods
A hospital based cross sectional study was carried out in the Department Of Biochemistry and Institute of Nuclear Medicine and Allied sciences, Chittagong Medical College Hospital, which included one hundred and fifty (150) subjects aged between 18-60 years over a period of one year from June 2017- June 2018. Subjects of both the sexes were evaluated sonographically and were divided into two groups as NAFLD cases (n=80) and Non-NAFLD controls (n=70). Subjects were excluded if they tested positive for hepatitis B virus surface antigen or anti -hepatitis C virus antibody or were suffering from liver cirrhosis, Acute or chronic hepatitis, history of alcohol abuse, Type II DM and Pregnancy.

Data was collected using a pre-tested structured questionnaire containing all the variables of interest after taking informed and written consent. Using standard phlebotomy procedures 5 ml of fasting venous blood was drawn from the median-cubital vein in between 8 and 9 am. Blood taken into clean and dry test tubes were kept for clot formation. After centrifugation serum was separated and taken into eppendorf which was

then immediately transported to Biochemistry Laboratory for analysis.

Fasting plasma glucose was determined after enzymatic oxidation method and fasting serum insulin wasa two-site sandwitch immunoassay using direct chemiluminescent technology. Insulin resistance was calculated from fasting plasma glucose and fasting serum insulin values by Homeostasis Model Assessment-Insulin Resistance (HOMA-IR. Necessary permission was obtained be for commence the study.

Results

Complete clinical profile, US data and serum samples were available for 150 subjects out of which, 80 (53%) were NAFLD cases and 70 (47%) were Non-NAFLD subjects taken as controls [Fig: 1].Mean age was significantly higher in cases (35.05 ± 1.05 years) than controls (26.53 ± 1.02 years) [Table I, Table II]. Inspite of more number of females in the study population there was no association in the gender distribution [Table III]. Fasting plasma glucose, fasting serum insulin and HOMA-IR were significantly higher in cases than that of controls (p < 0.05) [Table IV]. Insulin resistance status was more prevalent among the subjects with NAFLD than normal healthy subjects without NAFLD and cases of NAFLD were 15.23 times more likely to have insulin resistance than healthy control without NAFLD (p < 0.001). Out of 80 NAFLD cases 90% (n =72) had insulin resistance with HOMA-IR >2.6 and 10% (n=08) had no insulin resistance [Table V].

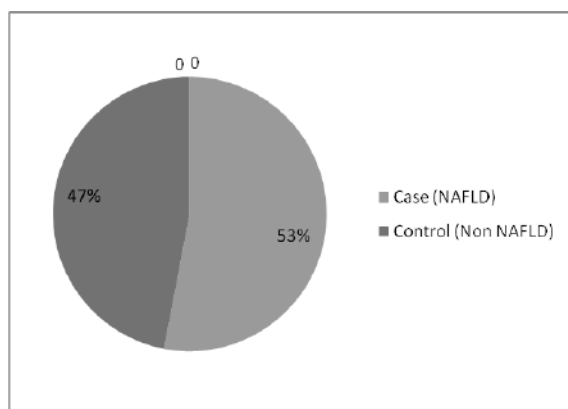**Figure 1** Distribution of study population by NAFLD status (n = 150)

Table I Distribution of the studypopulation by their age (n=150)

Age, in years	Cases (n=80)	Controls (n=70)	Total (n=150)
Mean ± SEM	35.05 ± 1.05	26.53 ± 1.02	31.07±0.81
Range	18 - 60	18 – 60	18-60

t value = 5.83, p = 0.00001[*].

Table II Distribution of the studypopulation by their age (n=150)

Age category (years)	NAFLD cases	Percentage (%)
18-29	22	27.5%
30-39	28	35%
40-49	25	31.25%
50-59	4	5%
≥60	1	1.25%
Total	80	100%

Table III Distribution of gender among the study population (n = 150)

Gender	Cases (n = 80)		Controls (n = 70)		Total	
	n	%	n	%	n	%
Male	35	44	32	46	67	44.67
Female	45	56	38	54	83	55.33

χ^2 value = 0.058, p = 0.81.

Table IV Comparison of fasting plasma glucose, fasting serum insulin level and HOMA-IR value amongst the study population (n=150)

Variables	Cases (n=80) (Mean ± SEM)	Controls (n=70) (Mean ± SEM)	p value	Significance
Fasting plasma glucose (mmol/l)	5.63 ± 0.67	5.45 ± 0.6	P = 0.02	Significant
Fasting serum insulin (mIU/L)	19.00 ± 0.61	12.8 ± 0.73	p < 0.00001	Significant
HOMA-IR	4.77 ± 0.16	3.13 ± 0.19	p < 0.0001	Significant

Table V Association between NAFLD and insulin resistance status (HOMA-IR) amongst the study population (n = 150)

Groups	Category of HOMA-IR		Total	Odds ratio (95% confidence interval)	p value & test statistic
	HOMA-IR >2.6	HOMA-IR ≤2.6			
NAFLD (Cases)	72 (90%)	08 (10%)	80	15.23 (6.34-36.59)	χ^2 = 46.05 p < 0.001 Significant
Non-NAFLD (Controls)	26 (37%)	44 (63%)	70		
Total	98 (65%)	52 (35%)	150		

Discussion

NAFLD is a spectrum of conditions associated with lipid deposition in hepatocytes and ranges from non-alcoholic steatohepatitis to advanced fibrosis and cirrhosis. It is strongly associated with obesity and insulin resistance and is currently considered by many as the hepatic component of the metabolic syndrome.[16,17] Insulin resistance appears to be an intrinsic defect in NAFLD patients.[11]

Insulin resistance between cases and controls were compared. It was found that insulin resistance was more among the cases than controls. Association between NAFLD and HOMA-IR status among the study population showed odds ratio 15.23 which was statistically significant, p = < 0.001. Other independent variables such as fasting serum insulin (p<0.00001), HOMA-IR (p<0.0001) were significantly higher in cases than that of controls. The result was similar to other research work done by E. Bugianesi et al.[11]

The results of the present study were similar to other previous research works by authors Yoosoo, Kelley DE, Sampath kumar.V et al, Rushad Patel et al and other relevant studies, other authors failed to demonstrate an association between other components of Insulin resistance with NAFLD.[18,15,6,11,19-22]

Limitation

The study has certain limitations which includes short duration of time, small sample size, cross sectional study and not assessing NAFLD by Liver biopsy.

Conclusion

The study revealed that there was positive association of insulin resistance with NAFLD.

Recommendations

Further prospective multicenter study in large scale is necessary to better understand the biochemical strategy of inflammatory markers for the development of NAFLD

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Author's contribution

Whole study was performed by the author himself.

Disclosure

The author declared no conflicts of interest.

References

1. Ludwig J, Viggiano TR, Mc Gill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo ClinProc. 1980; 55:434–438.

2. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. Gastroenterology. 1999; 116:1413–1419.

3. Hanley, Anthony J.G. et al. Elevations in Markers of Liver Injury and Risk of Type 2 Diabetes: The Insulin Resistance Atherosclerosis Study, Diabetes. 2004;53(10):2623.

4. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: A metabolic pathway to chronic liver disease. Hepatology. 2005; 42: 987-1000.

5. Marchesini G, Brizi M, MorselliLabate AM, Bianchi G, Bugianesi G, McCullough AJ. Association of non-alcoholic fatty liver disease to insulin resistance. Am J Med. 1999;107:450–455.

6. Chang WC, Bum SK, Yong KC, Ki CS, Ji Cheol B, Tae WK. Effect of Nonalcoholic Fatty Liver Disease on the Development of Type 2 Diabetes in Nonobese, Nondiabetic Korean Men. Gut and Liver. 2012;6(3):368-373.

7. Angulo P, Lindor KD. The natural history of non-alcoholic fatty liver disease: A population based cohort study. Gastroentrology Hepatology 2002; 17.

8. Marchesini G M B, Forlani G, Melchionda N. Am. J. Med. 1999;107:450–455.

9. Dabhi AS, Brahmbhatt KJ, Pandya TP, Thorat PB, Shah MC. Non-Alcoholic Fatty Liver Disease (NAFLD). Journal, Indian Academy of Clinical Medicine. 2008;9(1):36-41.

10. Marchesini G, Brizi M, Morselli-Labate AM et al. Association of non-alcoholic fatty liver disease to insulin resistance. AmJ Med. 1999;107:450–455.

11. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: Sites and mechanisms. Diabetologia. 2005;48: 634–642.

12. Chitturi S, Abeygunasekera S, Farrell GC et al. NASH and insulin resistance: insulin secretion and specific association with the insulin resistance syndrome. Hepatology. 2002; 35:373–379.

13. Marchesini G, Brizi M, Bianchi G et al. Non alcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001; 50:1844–1850.

14. Anna L, Luca V, Elisabetta B, Marco A, Agostino C, Ester V et al. Risk of Severe Liver Disease in Nonalcoholic Fatty Liver Disease with Normal Aminotransferase Levels. 2008; 48(3):792-798.

15. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: Relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol Endocrinol Metab. 2003; 285: E906-E916.

16. Choudhury J, Sanyal AJ. Clinical aspects of fatty liver disease. Semin Liver Dis. 2004;24:349-362.

17. Anoop MUS. Obesity and Dyslipidemia in South Asians.Nutrients. 2013;5:2708-2733.

18. Yoosoo C, Seungho R, Eunju S, Yumi J. Higher Concentrations of Alanine Aminotransferase within the Reference Interval Predict Nonalcoholic Fatty Liver Disease. Clinical Chemistry. 2007;53(4):686-692.

19. Babu R R, Sampath K V, Rama R J, Ambica D K. Study of biochemical markers in non alcoholic fatty liver disease. International Journal of Pharmacy and Biological Sciences. 2012;2(2):1-7.

20. Rushad P, Rupaldosi, Harshal J, Smith S, Purav S, Sarfaraz J. Non-Alcoholic Fatty Liver Disease (NAFLD) in Obesity. Journal of Clinical and Diagnostic Research. 2014 Jan, Vol-8(1): 62-6662.

21. Kamran Q, Ronald H. C, Fahad S, Gary A. Abrams. Comparative Evaluation of Whole Body and Hepatic Insulin Resistance Using Indices from Oral Glucose Tolerance Test in Morbidly Obese Subjects with Non-Alcoholic Fatty Liver Disease. Journal of Obesity. 2010. Article ID 741521.

22. Minoru T, Yuji K, Fuminobu S, Sumihiko S, Yasufumi M, T S et al. Triglyceride is strongly associated with nonalcoholic fatty liver disease among markers of hyperlipidemia and diabetes. 2014.