*www.jmscr.igmpublication.org* *Impact Factor 1.1147*
*ISSN (e)-2347-176x*

Journal Of Medical Science And Clinical Research
IGM Publication An Official Publication Of IGM Publication

# Role of Insulin Resistance in Non Alcoholic Fatty Liver in Obese Type-2 Diabetic Subjects

Authors

**Dharmveer Sharma[1], Sanjeev Kumar Singh[1], Poonam Gupta[2]**

**Neelima Singh[1], Nivedita Singh[1]**

[1]Department of Biochemistry, J.A. Group of Hospitals & G.R. Medical College, Gwalior, M.P. India-474001

[2]Department of Medicine, S.R.N. Group of Hospitals & M.L.N. Medical College, Allahabad, U.P. India

Correspondence Author

**Dharmveer Sharma**

Department of Biochemistry

J.A. Group of Hospitals & G.R. Medical College,

Gwalior, M.P. India-474001

E mail: *dharmveersharma434@gmail.com*

ABSTRACT

*Non alcoholic fatty liver disease (NAFLD) is a fatty liver disease occurring in patients without alcohol consumption. It includes a broad spectrum of liver disease, from fatty infiltration, inflammation and cirrhosis and is associated with obesity, hyperlipidemia and diabetes mellitus.An increase in the BMI and levels of FBS, total cholesterol, triglycerides, HDL, LDL, VLDL, SGPT, ALP, GGT, fasting insulin and hs CRP level and a decrease in HDL was observed in non alcoholic fatty liver group. Obesity, hyperglycemia, dyslipidemia and elevated liver enzymes, fasting insulin and hs CRP level are seen more frequently in non alcoholic fatty liver in type-2 diabetic obese patients.*

***Keywords-*** *NAFLD, BMI, ALT, ALP, GGT.*

## INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) also describes a clinicopathological condition that is characterized by significant lipid deposition in the hepatocytes of the liver parenchyma in patients with no history of excessive alcohol consumption. The spectrum of this disease is broad, ranging from a simple steatosis to non alcoholic steatohepatotitis, fibrosis and cirrhosis. Obesity, insulin resistance and diabetes are well known risk factors for the development of a fatty liver [1,2]. Non-alcoholic fatty liver disease (NAFLD) is an entity that includes patients with simple steatosis (SS) and non-alcoholic steatohepatitis (NASH), which has the propensity of progressing to cirrhosis and hepatocellular carcinoma [3]. Insulin resistance (IR) plays the central pathogenetic role in both type 2 DM and NAFLD with the latter being considered as the hepatic manifestation of the metabolic syndrome [4]. Other non-invasive markers such as Homeostasis Model Assessment-Insulin (HOMA) Resistance level ≥3.0 and type IV collagen 7S ≥5.0 ng/ml were found to be more sensitive and specific for predicting the relevant diagnoses [5]. Another inflammatory marker, High-sensitivity C-reactive protein (hs-CRP) has given mixed results as a biomarker while interleukin-6 (IL-6) has been shown to distinguish differing disease states and independently correlates with fibrosis [6,7].

## MATERIAL AND METHOD

Subjects were selected from those attending the medical outpatient department of G.R. Medical College, Gwalior (MP). A total number of 500 cases were included in our study, diagnosis being based on ultrasonography. Out of these, 100 were non obese and non diabetic healthy controls and 400 were obese with type-2 diabetic patients of both sexes included in the study, excluded based on significant alcohol consumption (>20 g/day). A written informed consent was obtained from the patients. Approval for conducting the study was obtained from the institutional ethics committee of G.R. Medical College, Gwalior (MP). For measuring weight, subject was instructed to stand still in the platform, with the body weight evenly distributed between both the feet. After removing heavy clothing weight (Seca 803, digital scale, Germany) was measured to the nearest of 0.1 kg. Height was measured using stadiometer (Seca 206, Germany) with head held in Frankfort plane to the nearest of 0.1 cm. Body mass index (BMI) was calculated by the following formula; weight (kg)/height (m2).The patients were further evaluated by the measurement of BMI, fasting blood sugar, total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), fasting insulin, HOMA-IR, and hs-CRP .The data was entered and analyze into Statistical packages for social science (SPSS version 21.0). Frequency and percentages were computed for categorical variable were presented in pie graph. Mean and standard deviation were analysed for quantitative variables like age, BMI, FBS, TC, TG, LDL, HDL,VLDL, total bilirubin, ALT, ALP, GGT, fasting insulin and HOMA-IR. Independent sample t test was used to compare mean of all the

quantitative variables between the two groups of patients were 0.001 level was considered significant. Correlation coefficient analysis was performed for risk factors of nonalcoholic fatty liver. P value less than 0.05 was considered statistically significant.

## RESULTS

The study included 400 patients of type 2 diabetes mellitus obese subjects and 100 healthy controls. This original research work approve by ethical committee. The average age of the patients was 52 ± 8 years (Ranging from 36 to 74). Thirty nine (39%) were males and Sixty-one (61%) were females. The values of all these biochemical study parameters except HDL were elevated in fatty liver disease patients as compared to non fatty liver disease group and the differences were found to be statistically significant (P value <0.01 and <0.001 ). Body mass index and triglycerides were positively correlated with fatty liver.

## DISCUSSION

The prevalence of NAFLD is high in conditions associated with insulin resistance, such as obesity, type-II diabetes mellitus, dyslipidemia and the metabolic syndrome [8]. The presence of NAFLD correlates significantly with BMI [9]. In our study only BMI was taken as a marker for obesity, raised BMI showed strong correlation with presence of fatty liver. In diabetic fatty liver group, the mean BMI was 33.85± 3.79 where as in non-fatty liver group it was 22.6±1.88 (P value< 0.01). In literature, among severely obese patients with diabetes, the prevalence of NAFLD has been found to be 100 % [10]. Obesity, especially visceral obesity, is frequently associated with NAFLD and their coexistence in the same individual increases the likelihood of having more advanced forms of liver disease. NAFLD occurs in 60% -95% of people with obesity [11]. The relationship between fatty liver, impaired glucose tolerance, diabetes mellitus and hyperlipidemia is well established. It has been demonstrated that insulin resistance leads to higher free fatty acid load to the liver, consequently higher triglyceride synthesis and increased secretion of triglyceride rich very low density lipoprotein (VLDL) from the liver. Hypertriglyceridemia have been also strongly correlated with liver fat accumulation [10, 12, 13]. Our study showed FBS levels in fatty liver disease group were higher than healthy control group, which confirmed the obvious dysglycemia in these patients (P value 0.001). We also found that increased triglyceride levels (mean 263.7±55.05) in diabetic fatty liver group as compared to control healthy group (triglycerides mean 122.09±19.49) and the results were statistically significant (P value <0.001). In a correlation coefficient analysis triglycerides were also found to be increase in obese type 2 diabetic obese nonalcoholic fatty liver population. The study was conducted in China also found that fatty liver positively correlated with plasma triglyceride levels and negatively with plasma HDL-C level [14]. In our study also, the elevated total cholesterol positively correlated with fatty liver disease. The levels of ALT, ALP and GGT were also elevated in obese type 2 diabetic fatty liver patients. This is also reported in other studies as well [15]. In this study, though raised ALT levels are taken as the first marker of fatty infiltration of the liver [16]. We also

noted the marked difference between the mean values of alkaline phosphatase in the two groups [17]. The mechanism behind the elevated liver enzymes in NAFLD patients is that dyslipidemia and insulin resistance leading to lipid deposition in hepatocytes causes induction of mitochondrial swelling, increased lysosomal fragility and impaired membrane integrity, resulting ultimately in the release of hepatic enzymes from the injured hepatocytes [10]. Patients with type-II diabetes mellitus have normal or increased levels of insulin; they are resistant to peripheral action of this hormone [18]. Deficiency of insulin promoting lipolysis, is an important cause of fatty liver in patients with poorly controlled diabetes mellitus. In this situation, massive lipolysis results in marked mobilization of free fatty acids, which are taken up by the liver and used for triglyceride synthesis with the consequent hepatic accumulation leading to steatosis. This cellular damage with subsequent inflammation may result in cellular death and fibrosis. Free Fatty Acids have also been found to be elevated in liver tissue of obese patients. Thus although diabetes mellitus and obesity may lead to increased liver fibrosis through different mechanism, the effect of these two conditions may be additive when they both exist in the same individual [10]. Insulin resistance induces lipid peroxidation which activates inflammatory cytokines and facilitates the progression of simple steatosis to non-alcoholic steatohepatitis and hepatic fibrosis [19]. Marchesini et al have reported that insulin resistance as assessed by HOMA-IR to be higher in NAFLD cases as compared to controls largely due to increased insulin concentration with normal or near-normal glucose levels. However, our data indicated that insulin resistance was higher primarily due to higher fasting glucose levels. Further, this is in line with our finding that fasting blood glucose level was an independent predictor of NAFLD [20]. This discrepancy between our data and that of Marchesini et al indicates that the clinicopathological profile of Indian NAFLD patients may be somewhat different from that seen in other ethnic groups [20, 21]. Our study has got few limitations. The diagnosis of NAFLD in our study was based on ultrasonography and exclusion of the known causes of chronic liver disease, but this was not confirmed by liver biopsy.

## CONCLUSION

The prevalence of non alcoholic fatty liver is high in type 2 diabetic patients and obesity, dyslipidemia, dysglycemia, elevation of liver enzymes (ALT, ALP and GGT), insulin resistance and HOMA-IR is seen more frequently in fatty liver than in non fatty liver. The independently associated risk factors for diabetic fatty liver are the raised BMI and elevated levels of triglycerides.

## ACKOWLEDGEMENT

We would like to thank Dr. Sanjeev Kumar Singh his help to promote me paper writing.

## REFERENCES

1. Greenfield, Cheung O, Sanyal AJ: Recent advances in nonalcoholic fatty liver. Curr Opin Gastroenterol 24:320, 2008.

2. Kim JH, Kim JH. Metabolic significance of nonalcoholic fatty liver disease in non obese, non diabetic adults. AMA. 2004; 164: 2169-2175.
3. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT. Similarities and differences in outcomes of cirrhosis due to non-alcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43:682–689.
4. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N: Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001; 50:1844-50.
5. Shimada M, Kawahara H, Ozaki K. Usefulness of a combined evaluation of the serum adiponectin level, HOMA-IR, and serum type IV collagen 7S level to predict the early stage of nonalcoholic steatohepatitis. Am J Gastroenterol. 2007; 102:1931–8.
6. Tarantino G, Conca P, Pasanisi F, et al. Could inflammatory markers help diagnose nonalcoholic steatohepatitis. Eur J Gastroenterol Hepatol. 2009; 21:504–11.
7. Lemoine M, Ratziu V, Kim M. Serum adipokine levels predictive of liver injury in non-alcoholic fatty liver disease. Liver Int. 2009; 29:1431–8.
8. Angulo P. Non alcoholic fatty liver disease. N Eng J Med 2002; 346: 1221 – 31.
9. Salgodo Jr. W, Santos JS, Sankarankutty AK, Castro ESilva OD. Non-alcoholic fatty liver disease and obesity. Acta Cir Bras 2006; 21: 72 – 78.
10. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictor of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999; 30: 1356 – 62.
11. Wang Y, Zhou M, Lam KS, Xu A. Protective roles of adiponectin in obesity-related fatty liver diseases: mechanisms and therapeutic implications. Arq Bras Endocrinol Metabol.2009, 53(2):201-212.
12. Luyckx FH, Lefebve PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. Diabetes Metab 2000; 26: 98 – 106.
13. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with non alcoholic fatty liver disease. J Clin Invest 2005; 115: 1343-51.
14. Jin HB, Gu ZY, Yu CH, Li YM. Association of nonalcoholic fatty liver disease with type-II diabetes: clinical features and independent risk factors in diabetic fatty liver patients. Hepatobiliary Pancreat Dis Int 2005; 4: 389 – 92.
15. Deng HM, Xiao CQ, Par HL. Analysis of associated factors in type-II diabetic patients with fatty liver. J Clin Intern Med 2003; 20: 22 – 25.
16. Vazarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C et al. High alanine aminotransferase is associated with

decreased hepatic insulin sensitivity and predicts the development of type-II diabetes. Diabetes 2002; 51: 1889 – 95.

17. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37:1286-92.
18. Raz I, Eldor R, Cernea S, Shafrir E. Diabetes: insulin resistance and derangements in lipid metabolism. Care though intervention in fat transport and storage. Diabetes Metab Res Rev 2005; 21: 3 – 14.
19. Petta S, Muratore C, Craxi A. Non-alcoholic fatty liver disease pathogenesis: the present and the future. Digestive and Liver Disease 2009;41(9):615-25.
20. Marchesini G, Brizi M, Morselli Labate AM, Bianchi G, Bugianesi G, McCullough AJ, Forlani G, Melchionda N. Association of non-alcoholic fatty liver disease to insulin resistance. Am J Med. 1999; 107:450–455.
21. Duseja A, Das A, Das R, Dhiman RK,Chawla Y, Bhansali A, et al. The clinicopathological profile of Indian patients with nonalcoholic fatty liver disease (NAFLD) is different from that in the West. Dig Dis Sci 2007; 52 : 2368-74.