ORIGINAL ARTICLE

Biochemical Changes In Subjects With Fatty Liver: Is There A Link?

Syed Aown Raza Shah Bokhari[1], Taimur Hussain Babar[2], Sikandar Hayat Khan[3], Mariam Hasan[4], Muhammad Junaid Khan[5]

ABSTRACT:

Objective: To evaluate the biochemical markers including serum triglycerides, ALT, and fasting plasma glucose in detection of fatty liver disease.

Methodology: This cross-sectional analysis was carried out at the department of radiology & pathology, PNS Rahat hospital, Karachi between March-2010 to February-2011.Sixty-two subjects with an ultrasonographic diagnosis of fatty liver were compared with thirty-seven subjects with normal ultrasound for fatty liver, after excluding all other abnormalities on history and examination. The comparison included measurement of biochemical abnormalities including fasting blood glucose, triglycerides, total cholesterol and alanine transaminase (ALT).

Results: The results of fasting blood glucose[{Fatty liver group=7.06 ± 3.51mmol/L}{Without fatty liver disease=5.12 ± 0.56 mmol/L} (p = 0.002)], serum triglycerides [{Fatty liver group=2.56 ± 1.33 mmol/L } {Without fatty liver disease=1.68 ± 0.97 mmol/L } (p = 0.001)] and ALT[{Fatty liver group=36.37 ± 18.12 IU/L} {Without fatty liver disease=28.15 ± 13.95 IU/L} (p = 0.026)] were significantly higher in subjects with fatty liver disease. The Receiver Operating Curve (ROC) analysis showed fasting blood glucose and serum triglycerides to have the most area under the curve (AUC) as 0.747 (95% CI: 0.647-0.847) and 0.731(95% CI: 0.622-0.840); while the other parameters have AUCs as: Serum ALT-0.650 (95% CI: 0.532-0.767) and total cholesterol-0.509 (95% CI: 0.389-0.629).

Conclusion: Hyperglycemia and hypertriglyceridemia are associated with an ultrasonographic diagnosis of fatty liver. Raised transaminase levels in subjects with fatty liver disease also suggest underlying hepatocyte damage.

Keywords: Fatty liver, Serum triglycerides, Serum ALT, Fasting plasma glucose.

INTRODUCTION:

With the emergence of obesity pandemic across the world, problems like nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and steatosis (fatty liver) are increasingly being encountered.[1] The presence of hepatic fat becomes not only a source of confusion during the diagnostic testing of an apparently healthy subject, but it also amounts to unnecessary stress to the patients leading to loss of technical man hours and most importantly not becoming a cost-effective option because of multiple requests for hepatitis screening and radiological investigations like repeated ultrasonography.[2]

Fatty deposition in liver has been related to excess of lipids travelling in the blood.[3,4] A lot of literature dealing with various aspect of this fat deposition states in liver has been available over the last decade.[4,5] However, the literature review will demonstrate some contrasts: Firstly, serum alanine transaminase (ALT) being a marker of hepatocyte injury has not been reported to be raised in subjects with such a diagnosis.[6,7] Secondly, there are studies which have shown variable results for differences in cholesterol and triglycerides among subjects with or without a fatty liver.[8] Thirdly, literature review does suggest that fat deposition in the liver may be due to associated insulin resistance or simply a complication of diabetes mellitus.[9] On the other side, the contrasting evidence also exists with regards to normoglycemia in a patient with underlying fat deposition in the liver.[10] Lastly, there are regional and ethnic differences which could play a differential role in associated development of fatty liver state and its associated biochemical picture.[11] A study was therefore planned to compare the results of glucose, ALT and lipid indices among subjects with and without a diagnosis of fatty liver.

✉ **Dr. Syed Aown Raza Shah Bokhari**
Consultant Radiologist
Department of Radiology
PNS Rahat Hospital
Karachi
✉ **Dr. Taimur Hussain Babar**
Consultant Radiologist
Department of Radiology
PNS SHIFA Hospital & BUMDC
Karachi
✉ **Dr. Sikandar Hayat Khan**
Chemical Pathologist
Department of Pathology
PNS Rahat Hospital
Karachi
Email: sik_cpsp@yahoo.com
✉ **Dr. Mariam Hasan**
Consultant Radiologist
Department of Radiology
KRL, Hospital
Karachi
✉ **Muhammad Junaid Khan**
Health Care Administrator
Department of Admin
PNS Rahat Hospital
Karachi
Received: 27-05-2016
Revised: 05-12-2016
Accepted: 20-12-2016

METHODOLOGY:

This comparative cross-sectional study was carried out at the department of radiology and pathology, PNS Rahat hospital, Karachi between March-2010 to February-2011. The target population was adult subjects presented

to the department of pathology for estimation of fasting blood glucose on clinical suspicion of underlying diabetes mellitus. The inclusion list was shortlisted by excluding subjects (n=201)who were admitted, had fever or associated acute stress, acute exacerbation of some metabolic disorder, or who did not volunteer because of their commitments. A total of 304 individuals were requested to undergo further study by visiting lab in exact medical fasting status on any working day after verbal explanation of study's nature. Only 116 subjects reported for sampling till end of January-2011. On the day of lab visit, the subjects were consented about study participation, later physical examination was conducted and interviewed for the presence of history of any metabolic disorder in self and family members (parents, brothers and sisters). Afterwards these subjects were sampled for 10 ml of blood for estimation of fasting blood glucose, total cholesterol, triglycerides and ALT. After phlebotomy procedure the subjects were sent to department of radiology for ultrasonographic examination. Subjects who were detected to have an associated diagnosis on ultrasound examination were further excluded (n=19) from the study.

Ultrasongraphic Examination: Ultrasound Liver was done in supine position in fasting patients on Sonoline Ultrasound grey scale machine using 5 MHz convex probe.

Lab Analysis: Blood glucose was analyzed by hexokinase method, triglycerides by GPO-PAP method, cholesterol by CHOD-PAP method and ALT was analyzed by UV kinetic method. The instrument used in lab for analysis was Hitachi-902 (clinical chemistry analyzer).

Statistical Analysis: The data was entered into SPSS version-15. Descriptive statistics were calculated for age and gender differences. Inferential statistics required comparison of biochemical parameters including fasting blood glucose, serum total cholesterol, triglycerides and serum ALT among subjects diagnosed to have fatty liver disease or otherwise which were carried out by independent sample t-test. Binary logistic regression analysis was utilized to measure the effect of confounders like age and gender keeping fatty liver diagnosis as the dependent variable.

RESULTS:

Out of all studied cases sixty-two subjects had ultrasongraphic diagnosis of fatty liver and thirty-five subjects had normal liver on ultrasound examination. Age differences between subjects having fatty liver disease or otherwise was not significant [{Group-1: Subjects with fatty liver disease: 41.81±8.89}{Group-2: Subjects without fatty liver disease: 38.91±7.81}, (p=0.114)]. Out of 97 subjects, 42/70 males and 20/27 females had fatty liver diagnosis on ultrasongraphic examination. The frequency of finding fatty liver in hypertension, diabetes mellitus and ischemic heart disease in study subjects were 12/97, 18/97 and 9/97. The percentage of association of fatty liver disorder with metabolic diseases was 75% for hypertensive subjects (9/12), 77% in patients with underlying ischemic heart disease (7/9) and 100% with subjects with newly diagnosed diabetes mellitus. The differences between fasting blood glucose, triglycerides, total cholesterol and ALT are shown in figures 1-4. The Receiver operating curve (ROC) analysis shows fasting blood glucose and serum triglycerides to have the most area under the curve (AUC) as 0.747 (95% CI: 0.647-0.847) and 0.731(95% CI:0.622-0.840); while the other parameters have AUCs as: Serum ALT-0.650 (95% CI: 0.532-0.767) and total cholesterol-0.509 (95% CI: 0.389-0.629). Logistic regression analysis [Figure-5] did not reveal the effect of age and gender to be significant in the development of fatty liver.

Figure: 1

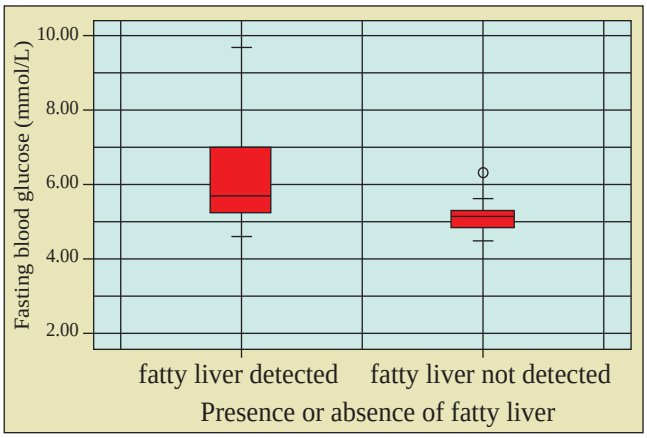

Figure-1: Differences in fasting blood glucose among subjects with fatty liver disease (7.06+3.51 mmol/L) and without fatty liver disease (5.12+0.56 mmol/L) [p=0.002].

Figure: 2

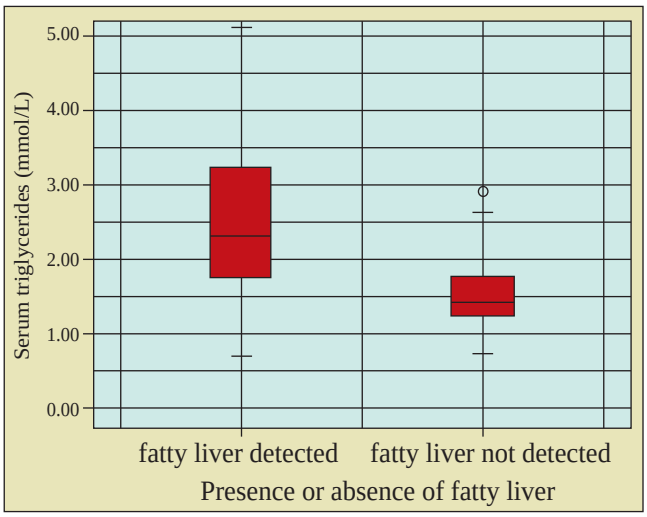

Figure-2: Differences in serum triglycerides among subjects with fatty liver diagnosis (2.56+1.33 mmol/L) and without fatty liver diagnosis (1.68+0.97 mmol/L) [p=0.001].

Figure: 3

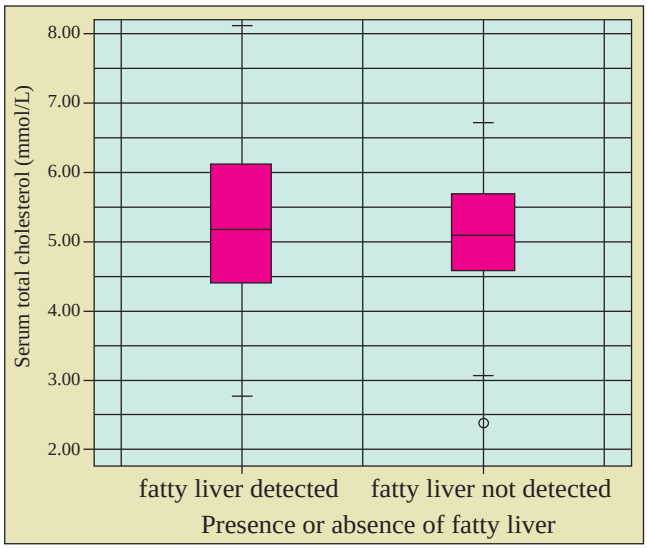

Figure-3: Differences in total cholesterol among subjects with fatty liver diagnosis (5.17+1.60 mmol/L) and without fatty liver diagnosis (4.96+0.95 mmol/L) [p=0.481].

Figure: 4

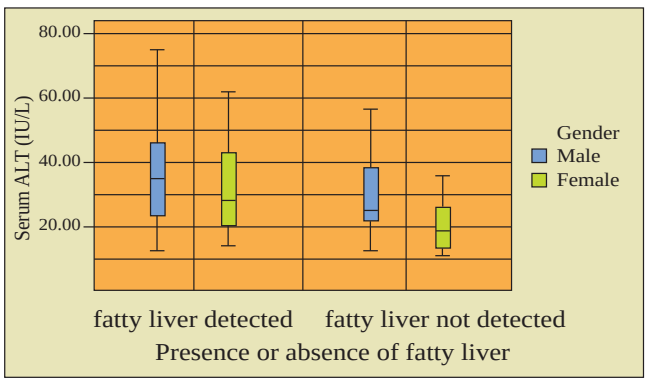

Figure-4: Differences in serum ALT among subjects with fatty liver diagnosis (36.37+18.12 IU/L) and without fatty liver diagnosis (28.15+13.95 IU/L) [p=0.026].

Figure: 5

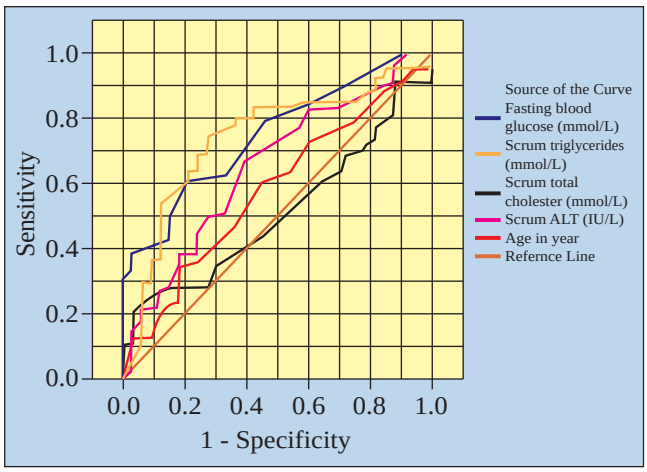

Figure-5: Receiver Operating Curve (ROC) analyais for fasting blood glucose, triglycerides, total cholesterol, ALT and age for predicting a fatty liver diagnosis.

DISCUSSION:

Our study has shown biochemical abnormalities especially hyperglycemia and hypertriglyceridemia are more frequent in subjects having an excessive fat deposition in the liver. The review of literature yields almost similar data.[3,12,13] Some studies have also demonstrated hypercholesterolemia to be associated with a diagnosis of fatty liver,[14] but we have not observed significant cholesterol differences among subjects with or without hepatic fat deposition. The explanation to this finding could be the fact that total cholesterol mainly constitutes lipoprotein bound cholesterol.These lipoprotein cholesterol in medically fasting state represent more often a depiction of hepatic lipoprotein efflux of low density lipoproteins and high density lipoproteins.[15] An insight into the fatty liver pathogenesis indicates association with higher intake of refined carbohydrates and diets rich in saturated fats.[16] These identified etiological players usually result in higher prevalence in lipoproteins containing an excess of triglycerides and may not initially disturb the other lipoprotein cholesterols in outset.[17] Upon uptake by hepatocytes, these fatty acids result in various states starting from simple ultrasongraphic evidence of extra fat in the liver to histopathological demonstration of steatohepatitis.[18] The above patterns of dyslipidemia, hyperglycemia and liver part i.e., fatty liver may be part of the wider entity of metabolic syndrome, which has a commoner metabolic basis of insulin resistance.[9] Moreover, there are studies which show observations similar to our findings in having non-significant cholesterol rise with fatty liver disease.[19] Another study by Singh et al suggests that cholesterol related differences are more encountered during the later stage of hepatic fat deposition.[20] The fact that some normoglycemic subjects also have fatty liver disease also prompts us in finding other etiological agents in the causation of this problem.[21,22] Serum alanine transaminase levels between subjects with or without fatty liver disease were not found to be significantly different. Canbakan et al have shown that hepatocytes not undergoing oxidative stress and apoptosis will probably not have an associated transaminase elevation.[23] Similarly, some other studies have demonstrated minimal transaminase differences between subjects with or with fatty deposition in the liver.[6,7,24,25] While the studies demonstrating the contrast are also available in literature.[26,27] The probable reasons to variable transaminase differences are because of evolution of disease from the stage of simple hepatic steatosis to a disease causing hepatitis and finally cirrhosis.[28] Studies have also indicated that raised serum transaminase levels may be due to associated insulin resistance in studied subjects independently of presence of hepatic steatosis.[29] Few limitations to our study must be acknowledged: Firstly, the study was a cross-sectional trial based upon non-probability convenience sampling, targeting the biochemical changes between subjects with or without fatty liver disease. Secondly, type-II error due to a small sample size can also be anticipated. It is also felt that the nature of our hospital based survey, being a cross-

sectional design should lead to a comprehensive epidemiological survey to augment or disapprove our observations.

The study may have important clinical implications: The trend of urbanization and changes in healthier life styles has led to the appearance of vast majority of asymptomatic human subjects who are diagnosed to have no other abnormality except fat deposition in the liver. Our study has demonstrated that such a random finding in apparently healthy subjects merits screening for ruling out any metabolic abnormalities like diabetes mellitus or hypertension.

CONCLUSION:

Hyperglycemia and hypertriglyceridemia are associated with an ultrasonographic diagnosis of fatty liver. Raised transaminase levels in subjects with fatty liver disease also suggest underlying hepatocytes damage.

REFERENCES:

1. Chitturi S, Wong VW, Farrell G. Nonalcoholic fatty liver in Asia: Firmly entrenched and rapidly gaining ground. J Gastroenterol Hepatol. 2011Suppl 1:163-72
2. Tareen BT. Serum ALT. Professional Med J 2005;12(3): 304-7
3. Ayala I, Castillo AM, Adánez G, Fernández-Rufete A, Pérez BG, Castells MT et al. Hyperlipidemic chicken as a model of non-alcoholic steatohepatitis. Exp Biol Med (Maywood). 2009; 234(1):10-6
4. Oldenburg B, Pijl H. Abdominal obesity: metabolic complications and consequences for the liver. Ned Tijdschr Geneeskd. 2001;145(27):1290-4
5. Cortez-Pinto H, Camilo ME, Baptista A, De Oliveira AG, De Moura MC. Non-alcoholic fatty liver: another feature of the metabolic syndrome? Clin Nutr. 1999 ;18(6):353-8
6. Taseer HI, Hussain L, Safdar S, Mirbahar MA, Ahmad I. Frequency of nonalcoholic fatty liver disease (NAFLD) and its biochemical derangements in type-2 diabetic patients. Pak J Med Sci 2009;25(5):817-20
7. Zelber-Sagi S, Lurie Y, Nitzan-Kaluski D, Halnern Z, Oren R. Serum ALT is not a reliable screening tool for NAFLD in the general population. Journal of Hepatology 2006;44:S267
8. Khurram M, Shakoor A, Arshad MM, Khaar BH, Hasan Z. Characteristic features of 50 NAFLD patients. Rawal Med J 2004;29(1):8-12
9. Sung KC, Kim SH. Interrelationship between fatty liver and insulin resistance in the development of type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism 2011;96(4):1093-7
10. Narasimhan S, Gokulakrishnan K, Sampathkumar R, Farooq S, Ravikumar R, Mohan et al. Oxidative stress is independently associated with non-alcoholic fatty liver disease (NAFLD) in subjects with and without type 2 diabetes. Clin Biochem. 2010 ;43(10-11):815-21
11. 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(9):2368-74
12. Akahoshi M, Amasaki Y, Soda M, Tominaga T, Ichimaru S, Nakashima E, et al.Correlation between fatty liver and coronary risk factors: a population study of elderly men and women in Nagasaki, Japan. Hypertens Res. 2001;24(4):337-43
13. Yamada T, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. J Gastroenterol Hepatol. 2010;25(2):352-6
14. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. J Clin Gastroenterol. 2006;40(8):745-52
15. Lucero D, Zago V, López GI, Graffigna M, López GH, Fainboim H, et al. Does non-alcoholic fatty liver impair alterations of plasma lipoproteins and associated factors in metabolic syndrome? Clinica Chimica Acta. 2011 ;412(7):587-92
16. Panchal SK, Poudyal H, Iyer A, Nazer R, Alam A, Diwan V, et al. High-carbohydrate high-fat diet–induced metabolic syndrome and cardiovascular remodeling in rats. J Cardiovasc Pharmacol. 2011;57(1):51-64
17. Zago V, Lucero D, Macri EV, Cacciagiú L, Gamba CA, Miksztowicz V, et al. Circulating very-low-density lipoprotein characteristics resulting from fatty liver in an insulin resistance rat model. Ann Nutr Metab. 2010;56 (3):198-206
18. Aller R, de Luis DA, Fernandez L, Calle F, Velayos B, Olcoz JL, et al. Influence of insulin resistance and adipokines in the grade of steatosis of nonalcoholic fatty liver disease. Dig Dis Sci. 2008;53(4):1088-92
19. Simonen P, Kotronen A, Hallikainen M, Sevastianova K, Makkonen J, Hakkarainen A, et al. Cholesterol synthesis is increased and absorption decreased in non-alcoholic fatty liver disease independent of obesity. J Hepatol. 2011;54(1):153-9
20. Singh DK, Sakhuja P, Malhotra V, Gondal R, SarinSK. Independent predictors of steatohepatitis and fibrosis in Asian Indian patients with non-alcoholic steatohepatitis. Dig Dis Sci. 2008;53(7):1967-76
21. Liu S, Shi W, Li G, Jin B, Chen Y, Hu H. Plasma reactive carbonyl species levels and risk of non-alcoholic fatty liver disease. Journal of gastroenterology and hepatology 2011;26(6):1010-5
22. Hooper AJ, Adams LA, Burnett JR. Genetic determinants of hepatic steatosis in man. J Lipid Res. 2011;52(4):593-617
23. Canbakan B, Senturk H, Canbakan M, Toptas T, Tabak O, Balci H, et al. Is alanine aminotransferase level a surrogate biomarker of hepatic apoptosis in nonalcoholic fatty liver disease? Biomark Med. 2010;4(2):205-14
24. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005;22(9):1141-5
25. Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology. 2008 ;48(3):792-8
26. Magosso E, Ansari MA, Gopalan Y, Abu Bakar MR, Karim Khan NA, Wong JW, et al. Prevalence of non-alcoholic fatty liver in a hypercholesterolemic population of northwestern peninsular Malaysia. Southeast Asian J Trop Med Public Health. 2010;41(4):936-42
27. Su HM, Zhang ZX, Pan L, Guo YR, Liu YK, Zhang Q.

Metabolic characteristics of a fatty liver disease model induced by high-fat feeding in young rats. ZhonghuaGan-Zang Bing ZaZhi. 2010;18(1):54-8 doi: 10.3760/cma.j.issn.1007-3418.2010.01.013

28. Rodríguez-Hernández H, Gonzalez JL, Márquez-Ramirez MD, Flores-Hernandez M, Rodríguez-Morán M, Guerrero-Romero F. Risk factors associated with nonalcoholic fatty liver disease and its relationship with the hepatic histological changes. Eur J Gastroenterol Hepatol. 2008;20(5):399-403
29. Esteghamati A, Noshad S, Khalilzadeh O, Khalili M, Zandieh A, Nakhjavani M. Insulin resistance is independently associated with liver aminotransferases in diabetic patients without ultrasound signs of nonalcoholic fatty liver disease. Metab Syndr Relat Disord 2011;9(2):111-7