



## Correlation of Obesity and Other Factors with Presence of Extra Hepatic Disease among the Patients Presenting with Fatty Liver

Muhammad Abdul Quddus<sup>1\*</sup>, Muhammad Farid Khan<sup>1</sup>, Rizwan Saeed Kiyani<sup>1</sup>, Atif Abbas<sup>2</sup>, Qurat-Ul-Ain<sup>2</sup> and Fauzia Khan<sup>3</sup>

<sup>1</sup> Poonch Medical College, AK CMH/Sheikh Khalifa Bin Zayad Al Nahyan Hospital, Rawalakot, Pakistan

<sup>2</sup> Fauji Foundation Hospital, Rawalpindi, Pakistan

<sup>3</sup> HITEC Institute of Medical Sciences, Taxila, Rawalpindi, Pakistan

\*Corresponding e-mail: [aquddus1@gmail.com](mailto:aquddus1@gmail.com)

### ABSTRACT

**Purpose:** To assess the Correlation of obesity and other factors with presence of extrahepatic disease among the patients presenting with fatty liver at CMH Rawalakot, Azad Kashmir. **Study design:** Correlational Study. **Setting:** Gastroenterology department CMH//Sheikh Khalifa Bin Zayad Al Nahyan Hospital Rawalakot. **Duration of study:** Six months, from 01-09-2018 to 01-03-2019. **Patients and methods:** A prospective study was conducted on 51 patients of fatty liver diagnosed on ultrasound by consultant radiologist of own hospital. The demographic profile included age, gender, presence of obesity, triglyceride levels and total cholesterol levels. Common extra-hepatic conditions which were looked for in this study included Diabetes mellitus (DM), Hypertension (HTN), Ischemic heart disease (IHD) and Osteoarthritis (OA) which were diagnosed with the help of detailed history taking, relevant physical examination and laboratory investigations. **Results:** Out of 51 patients included in the final analysis 31 were male and 20 were female. Twenty-seven participants had one or more co-morbid illnesses while 24 had no such diseases at the time of study. DM was the commonest comorbid illness while OA was least reported. Twenty four patients were obese while 27 had BMI less than 30. The presence of obesity and raised total cholesterol levels had a significant relationship with presence of extra-hepatic illness among the patients presenting with fatty liver. **Conclusion:** Patients presenting with fatty liver have high prevalence of extrahepatic diseases. Routine screening of common illnesses should be done on all the patients who have been diagnosed as having a fatty liver. Special attention should be given to the patients who had BMI more than 30 or raised total cholesterol levels.

**Keywords:** Extra-hepatic disease, Fatty liver, Obesity

### INTRODUCTION

Liver pathologies are one of the biggest causes of mortality and morbidity among patients all over the world [1]. Various metabolic and infective causes may alter the function of this vital organ and cause symptoms which can be distressful for the patient and may lead to serious consequences [2]. Fatty liver has been one of the most common metabolic diseases of this organ which has been a cause or consequence of underlying liver malfunctioning [3]. It is usually diagnosed incidentally on radiological investigations on suspected when liver enzymes have been raised in absence of the other pathologies related to liver [4].

Non-alcoholic fatty liver disease (NAFLD) has been associated with various diseases outside the liver. The bi-modal relationship of these diseases with fatty liver has been under discussion of clinicians and researchers for long [5] Diabetes mellitus (DM), Ischemic heart disease (IHD), Chronic kidney disease (CKD) and various cancers have been linked with the presence of fatty liver or non-alcoholic fatty liver disease in various studies done on this subject all over the world [6]. It has been important in various aspects that either these diseases involved liver in the process of

illness due to their etiopathogenesis or it is liver pathology which gave rise to the factors which lead to these illnesses [7].

Obesity has been a major health problem worldwide [8]. Developed countries and the developing ones both have a high prevalence of this problem with different perspectives [8,9]. Obesity may lead to various systemic illnesses including Diabetes mellitus (DM), Hypertension (HTN), sexual problems, stroke, psychiatric problems and various cancers [10]. The liver has also been victim of this problem and metabolic syndrome often has fatty liver as comorbidity [11]. The fatty liver itself can also accelerate the process of obesity and activate multiple pathways which could lead to various metabolic derangements in the body. These metabolic derangements may be linked to pathogenesis of comorbid illnesses among the patients suffering from non-alcoholic fatty liver [12]. A recent review concluded that dyslipidemia among the patients of fatty liver may predispose them towards various cardiovascular problems including Hypertension (HTN), Ischemic heart disease (IHD) [13]. Another interesting study with cross-sectional design revealed a strong association among liver fat contents, Low-density lipoprotein (LDL) particle size, and Apolipoprotein B/A-I levels. It was stated that this dyslipidemia may be derived from liver fat instead of obesity and markers of obesity in the other parts of the body. Diabetes has also been a well-studied risk factor for the presence of fatty liver so this comorbidity is not uncommon [14]. A relatively new finding is the link of fatty liver with decreased bone mineral density and increased chances of developing osteoarthritis during the course of non-alcoholic fatty liver disease [15].

Considering the impact of fatty liver on obesity increased incidence of extrahepatic diseases in these patients, it becomes necessary for the health professionals of a developing country like ours to screen the patients in time for all the problems and implement principles of primary and secondary prevention in order to lessen the burden on health budget of the country. Both obesity and non-alcoholic fatty liver disease are common diseases in our setup with increasing prevalence with each year [9,16]. Few epidemiological studies have been done in this regard but no study so far conducted to assess the variety of comorbid illness present among these patients especially in the region of Azad Jammu and Kashmir. We, therefore, planned this study with the rationale to assess Correlation of obesity and other factors with presence of extrahepatic disease among the patients presenting with fatty liver at CMH/Sheikh Khalifa Bin Zayad Al Nahyan Hospital Rawalakot.

#### **PATIENTS AND METHODS**

This prospective correlational study was conducted at the Gastroenterology department of Poonch medical college Rawalakot affiliated teaching hospital CMH/Sheikh Khalifa Bin Zayad Al Nahyan Hospital Rawalakot from 01-09-2018 to 01-03-2019. The sample was gathered by using the non-probability consecutive sampling technique. All patients between the age of 18 and 60 years diagnosed as suffering from fatty liver on routine ultrasonography by consultant radiologists were included in the study. Ultrasound is cost-effective and easy to perform technique especially in remote areas of Kashmir where biopsy of every patient has not been possible. It has sensitivity of more than 90 percent if hepatic steatosis is more than 30 percent. To remove the bias of operator dependence, one consultant performed all the ultrasounds of cases included in this study [17] Obesity was labeled by using the routine BMI formula and classes made by WHO. BMI more than 30 were taken as significant obesity in this analysis as per guidelines [18]. Diabetes mellitus (DM), Hypertension (HTN), Ischemic heart disease (IHD) and Osteoarthritis (OA) were the comorbid diseases studied in this analysis and were diagnosed with the help of detailed history taking, relevant physical examination and laboratory investigations according to the recent guidelines. Intravenous blood samples were collected from cirrhosis patients with the help of 5 ml syringe. Serum was separated and stored at -40°C until analyzed for lipid profile and fatty acids by micro-lab 300 and gas chromatography (GC 8700, Perkin-Elmer Ltd). Lipid profile performed by kit method (Merck, Germany) included Total cholesterol (TC), Triacylglycerol (TAG), High-density lipoprotein-cholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C), Very low-density lipoprotein-cholesterol (VLDL-C) and total lipids. Hypocholesterolemia in our analysis was defined as: TC <100 mg/dl and/or HDL-cholesterol <40 mg/dl and/or LDL-cholesterol <70 mg/dl and for hypotriglyceridemia value of TG <70 mg/dl [19]. Exclusion criteria were patients with less than 18 years of age or those with unclear medical diagnosis along with fatty liver. Pregnant patients or those with other co-morbidities which were not included in this analysis were also not included in the study. Any major organ failure like lungs, liver or kidney was also part of exclusion criteria. Patients with Hepatitis B, Hepatitis C, Human Immunodeficiency Virus, vasculitis, history of

alcohol, other substance use or those who did not give written informed consent were also excluded from the study.

Ethical approval was taken from the ethical review board committee of Poonch Medical College Rawalakot before the start of this study. After written informed consent from the potential participants, patients with fatty liver in the Gastroenterology department of CMH/Sheikh Khalifa Bin Zayad Al Nahyan Hospital Rawalakot fulfilling the above-mentioned criteria of inclusion and exclusion were included in the study. Proper clinical and laboratory investigations like ECG, chest X-ray, cardiorespiratory status and serology were carried out before the inclusion. Once comorbidities were established and exclusion criteria were applied then the patients underwent ultrasound abdomen by the consultant radiologist. Patients diagnosed with fatty liver then underwent the lipid profile and Body mass index (BMI) calculation in addition to the relevant history, examination and laboratory investigations for the comorbidities under study [20].

All statistical analysis was performed by using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). The mean and standard deviation for the age of study participants was calculated. Frequency and percentages for gender, presence of obesity, deranged levels of total cholesterol and triglycerides and comorbidities were calculated. Binary logistic regression analysis was used to establish relationship between obesity and other factors with presence of extra hepatic disease among the patients presenting with fatty liver in this analysis.

## RESULTS

A total of 57 patients were initially approached to get them enrolled in the analysis. One had no clear diagnosis of the underlying medical condition, one was pregnant and one patient did not give consent to get include him in the study. Four were suffering from viral infections including Hepatitis C, Hepatitis B or Human Immunodeficiency Virus. Out of 51 patients included in the final analysis, 31 were male and 20 were female. Twenty-seven participants had one or more co-morbid illnesses while 24 had no such diseases at the time of study. Diabetes mellitus (DM) was the commonest comorbid illness while Osteoarthritis (OA) was least reported among the patients with fatty liver at CMH Rawalakot. Twenty Four patients were obese with body mass index (BMI) greater than 30 while 27 had body mass index (BMI) below 30 and were not classed as obese in this study (Table 1). When binary logistic regression analysis was applied on the data generated during the study period of six months, presence of obesity and high total cholesterol levels had a significant relationship with presence of extra-hepatic illness among the patients presenting with fatty liver (Table 2).

**Table 1 Characteristics of patients diagnosed as fatty liver on USG abdomen in our study N=51**

| Age (years)                    |                      |
|--------------------------------|----------------------|
| Mean $\pm$ SD                  | 37.21 ( $\pm$ 3.351) |
| Range (min-max)                | 19 years-57 years    |
| Gender                         |                      |
| Male                           | 31 (60.8%)           |
| Female                         | 20 (39.2%)           |
| Comorbid diseases              |                      |
| No                             | 24 (47.1%)           |
| Yes                            | 27 (52.9%)           |
| Frequency of comorbid diseases |                      |
| Diabetes Mellitus              | 16                   |
| HTN                            | 9                    |
| IHD                            | 7                    |
| Osteoarthritis                 | 5                    |
| Presence of obesity            |                      |
| Obese                          | 24 (47.1%)           |
| Non Obese                      | 27 (52.9%)           |

**Table 2 The correlated factors relating to presence of extrahepatic diseases among the patients with fatty liver: The binary logistic regression analysis**

| Variables   | p-value | Odds ratio | Confidence interval |         |
|---|---------|------------|---------------------|---------|
|   |         |            | Lower               | Upper   |
| Age (reference is <18-40 years)                             | 0.188   | 4.852      | 0.463               | 50.88   |
| Gender (reference is male)                                  | 0.805   | 0.784      | 0.114               | 5.409   |
| Obesity (reference is non-obese)                            | 0.009   | 26.481     | 2.253               | 311.275 |
| Triglyceride levels (reference is more than 70 mg/dl)       | 0.724   | 1.432      | 0.196               | 10.495  |
| Total cholesterol levels (reference is more than 100 mg/dl) | 0.04    | 14.385     | 1.13                | 183.186 |

## DISCUSSION

Medical illness other than liver-related sometimes becomes major trouble in management of the patients with liver disease [2] Fatty liver and Non-alcoholic fatty liver disease (NAFLD) has been one of the illnesses which come under this category. The unique pathophysiology of this disorder some time creates a positive feedback cycle which entangles the individual in various metabolic derangements resulting in number of diseases [4,5]. Overweight or obesity complicates the situation more. Sometimes it is metabolic syndrome which may lead to deposition of fat inside this vital organ of the body and sometimes it's the fat deposition in liver which alters the functioning capacity and leads to systemic illness including metabolic syndrome and other related problems [7,9]. This study, therefore, was planned with the rationale to assess Correlation of obesity and other factors with presence of extrahepatic disease among the patients presenting with fatty liver at a teaching hospital of Azad Jammu and Kashmir. Extrahepatic illnesses were highly prevalent in our target population. More than half of the patients with fatty liver suffered from one or another systemic illness usually of metabolic origin. These results are in accordance with the studies done in the recent past around the globe [11-13].

Diabetes mellitus (DM) was the commonest comorbid in our patients. This has been reported in the past as well [13]. Etiopathogenesis of fat deposition on the liver due to this multisystem metabolic illness has been a keen interest for researchers in the past [8]. It still is very hard to predict the exact direction of events i.e. from diabetes mellitus (DM) to fatty liver or from fatty liver to Diabetes mellitus (DM) but one thing is very clear that this comorbidity is very common. Though osteoarthritis (OA) was least reported still considerable number of patients in our study had suffered from osteoarthritis (OA). These results have been shown in past as well [15]. Fatty liver may cause metabolic changes and lead to decreased bone mineral density and accelerates the process of degeneration. Osteoarthritis (OA) also hinders in adopting lifestyle modifications required for obesity and fatty liver.

The presence of obesity had a strong relationship with presence of extrahepatic illness in our study upon application of regression analysis. Similar results have been generated by studies done on similar subjects [10,12]. The underlying pathogenesis of obesity and other metabolic diseases is quite similar and explains this association. It also emphasizes the common management goals which could reduce both the obesity and severity of extrahepatic illness among the patients with fatty liver.

Raised total cholesterol levels also emerged as a strong predictor for presence of extrahepatic disease among patients suffering from fatty liver. Literature published in past also had similar results [20]. The raised total cholesterol levels may be marker of both presence of fat in eh liver and metabolic extrahepatic illness. More research with control of confounding variables and sophisticated study design may generate generalizable results in this regard.

## CONCLUSION

Patients presenting with fatty liver have a high prevalence of extrahepatic diseases. Routine screening of common illnesses should be done on all the patients who have been diagnosed as having a fatty liver. Special attention should be given to the patients who had BMI more than 30 or raised total cholesterol levels.

## DECLARATIONS

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Asrani, Sumeet K., et al. "Burden of liver diseases in the world." *Journal of Hepatology*, Vol. 70, No. 1, 2018, pp.151-71.
- [2] Thanapirom, Kessarinn, et al. "The incidence, etiologies, outcomes, and predictors of mortality of acute liver failure in Thailand: a population-base study." *BMC Gastroenterology*, Vol. 19, No. 1, 2019, p. 18.
- [3] Shetty, Akshay, and Wing-Kin Syn. "Health and economic burden of non-alcoholic fatty liver disease in the United States and its impact on veterans." *Federal Practitioner*, Vol. 36, No.1, 2019, p. 14.
- [4] Tanaka, Naoki, et al. "Current status, problems, and perspectives of non-alcoholic fatty liver disease research." *World Journal of Gastroenterology*, Vol. 25, No. 2, 2019, p. 163.
- [5] Glass, Lisa M., et al. "Comorbidities and non-alcoholic fatty liver disease: The chicken, the egg, or both?" *Federal Practitioner*, Vol. 36, No. 2, 2019, p. 64.
- [6] Mikolasevic, Ivana, et al. "Nonalcoholic fatty liver disease-A multisystem disease?" *World Journal of Gastroenterology*, Vol. 22, No. 43, 2016, p. 9488.
- [7] Milić, Sandra, Davorka Lulic, and Davor Stimac. "Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations." *World Journal of Gastroenterology*, Vol. 20, No. 28, 2014, p. 9330.
- [8] Yu Chung Chooia, Cherlyn Dinga, and Faidon Magkos. "The epidemiology of obesity." *Metabolism*, Vol. 92, 2019, pp. 6-10.
- [9] Aamir, Azizul Hasan, et al. "Diabetes prevalence survey of Pakistan (DPS-PAK): Prevalence of type 2 diabetes mellitus and prediabetes using HbA1c: A population-based survey from Pakistan." *BMJ Open*, Vol. 9, No. 2, 2019, p. e025300.
- [10] Hruby, Adela, et al. "Determinants and consequences of obesity." *American Journal of Public Health*, Vol. 106, No. 9, 2016, pp. 1656-62.
- [11] Divella, Rosa, et al. "Obesity, non-alcoholic fatty liver disease and adipocytokines network in promotion of cancer." *International Journal of Biological Sciences*, Vol. 15, No. 3, 2019, p. 610.
- [12] Lee, Jeong In, et al. "The relationship between 10-year cardiovascular risk calculated using the pooled cohort equation and the severity of non-alcoholic fatty liver disease." *Endocrinology and Metabolism*, Vol. 31, No. 1, 2016, pp. 86-92.
- [13] Bril, Fernando, et al. "Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD." *The Journal of Clinical Endocrinology and Metabolism*, Vol. 101, No. 2, 2016, pp. 644-52.
- [14] Lee, Min-Kyung, et al. "Metabolic health is more important than obesity in the development of nonalcoholic fatty liver disease: A 4-year retrospective study." *Endocrinology and Metabolism*, Vol. 30, No. 4, 2015, pp. 522-30.
- [15] Targher, G., A. Lonardo, and M. Rossini. "Nonalcoholic fatty liver disease and decreased bone mineral density: is there a link?" *Journal of Endocrinological Investigation*, Vol. 38, No. 8, 2015, pp. 817-25.
- [16] Pati, Girish K., and Shivaram P. Singh. "Nonalcoholic fatty liver disease in South Asia." *Euroasian Journal of Hepato-Gastroenterology*, Vol. 6, No. 2, 2016, p. 154.
- [17] Khov, Nancy, Amol Sharma, and Thomas R. Riley. "Bedside ultrasound in the diagnosis of non-alcoholic fatty liver disease." *World Journal of Gastroenterology*, Vol. 20, No. 22, 2014, p. 6821.
- [18] Misra, Anoop, and Nikhil V. Dhurandhar. "Current formula for calculating body mass index is applicable to Asian populations." *Nutrition and Diabetes*, Vol. 9, No. 1, 2019, p. 3.
- [19] Boemeke, Laura, et al. "Lipid profile in cirrhotic patients and its relation to clinical outcome." *ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo)*, Vol. 28, No. 2, 2015, pp. 132-35.
- [20] Raiya Sarwar, Nicholas Pierce, and Sean Koppe. "Obesity and nonalcoholic fatty liver disease: current perspectives." *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, Vol. 11, 2018, p. 533.