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ORIGINAL ARTICLE

Correlation of Hepatic steatosis, Fibrosis and Body anthropometry.

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ABSTRACT... Objective: To determine the correlation of hepatic steatosis and fibrosis with body anthropometry among Non-alcoholic fatty liver disease (NAFLD) patients presenting in outpatients Gastroenterology clinics in a tertiary care hospital in Karachi, Pakistan. **Study Design:** Cross-sectional study. **Setting:** Department of Gastroenterology, Liaquat National Hospital, Karachi, Pakistan. **Period:** October 2022 to March 2023. **Methods:** Body anthropometric measures and demographic data of patients were recorded when presenting to outpatient clinics with NAFLD. The controlled attenuation parameter (CAP) was obtained by FibroScan using an M or XL probe considering CAP value ≥ 248 dB/m as hepatic steatosis. Liver fibrosis was defined as a liver stiffness (LS) value ≥8 kPa. **Results:** In a total of 300 patients, the mean age was 51.4±8.4 years. The median CAP was 251 (IQR=219-342). Steatosis was present among 233 (77.7%) patients. Fibrosis was present among 229 (76.3%) patients. Steatosis was found to have significant correlation with age, waist circumference, neck circumference, hip circumference, triglycerides, creatinine, low density lipoprotein, alinine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, srum cholesterol and, high density lipoprotein. Fibrosis was significantly correlated with age, waist circumference, neck circumference, hip circumference, triglycerides, low density lipoprotein, total bilirubin, alanine tansaminase, alkaline phosphatase, gamma-glutamyl transferase, serum cholesterol, high density lipoprotein. **Conclusion:** Considerable interplay of metabolic factors, and anthropometric measures exist with NAFLD. It is important to monitor visceral fat measurements among NAFLD patients with anthropometric and biochemical abnormalities.

Key words: Anthropometry, Fibrosis, Non-alcoholic Fatty Liver Disease, Steatosis, Visceral Fat.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is featured as unnecessary hepatic fat buildup, related to insulin resistance and defined by the steatosis existence in >5% of hepatocytes based on histological analysis or by a proton density fat fraction >5.6%.[1] The illness is wide spreading globally. It can progress from simple fat collection in liver to inflammation and injury to hepatocytes ultimately leading to cirrhosis.[2] While the NAFLD is affecting around a quarter of the population worldwide, Nonalcoholic steatohepatitis (NASH) is seen in around 1.5-6.5% in community masses.[3]

A part from the metabolic causes (like diabetes mellitus, hypothyroidism, dyslipidemia etc.) obesity is most common condition leading to hepatic steatosis. NAFLD is linked to metabolic comorbidities, such as fatness (51%), hyperlipidemia (69%), metabolic syndrome (42%), hypertension (39%) and type 2 diabetes (22%).[2] Different cut-off of body mass index (BMI) is used across the world to classify obesity and this classification varies across the world.[4] However, NAFLD is a frequent illness in lean individuals in the South Asia.[5]

Liver biopsy is supposed as the benchmark for detecting, measuring and staging hepatic illnesses of different pathologies. Fibroscan is an ultrasound based technology which is being used to assess hepatic fibrosis non-invasively.[6] Controlled attenuation parameter is a novel technology now incorporated in Fibroscan to measure hepatic steatosis. It uses the same validated measurements, criteria and signals which are used by Fibroscan for Liver stiffness measurements (LSM).[7,8] The controlled

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attenuation parameter CAP score and LS parameters relates hepatic steatosis degree ($r = 0.656$, $p<0.001$) and fibrosis ($r = 0.714$, $P<0.001$).[9] This fact along with the wide spread availability of Fibroscan, ease of operation, patient readiness and avoidance of risk associated with liver biopsy has almost replaced liver biopsy for the estimation of hepatic steatosis.

METHODS

The present cross-sectional study was performed in out-patient clinics of gastroenterology department in Liaquat National Hospital, Karachi Pakistan. The study was commenced during October 2022 to March 2023 following the approval from hospital ethics committee bearing letter number 788-2022-LNH-ERC. The study enlisted patients based on written informed consent through the use of non-probability consecutive sampling.

Assuming a correlation of 0.2[11] of steatosis with waist to hip ratio (WHR) at 80% power and 95% confidence interval with no correlation in null hypothesis and 10% drop out rate, yielded a sample size of 215 patients. Patients were enrolled using non-probability consecutive sampling technique. All patients presenting to gastroenterology department for the sake of Fibroscan were included in the study. Patients known to have chronic viral hepatitis, taking alcohol >30 g/day for men, >20 g/day for women), known causes of chronic liver disease like metabolic and, autoimmune liver diseases, patients with ascites or other pathologies preventing Fibroscan or hampering fibroscan findings were excluded from this study.

Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Waist circumference (WC) was measured as mid-point between lower costal margin and anterior superior iliac spine. Hip circumference (HC) was measured as the widest point over the buttocks. Measurement for neck circumference (NC) was made at midway of the neck i.e. just below Adam's apple along a parallel line with one decimal place observation. Patients investigations including total leukocyte count (TLC), random blood sugar (RBS), low density lipoprotein (LDL), high density lipoprotein (HDL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were also noted.

Fibroscan was used for obtaining CAP values with XL or M probe (Echosens, Paris, France). Technician with high skills and who was blinded to this study and patients' data carried out the procedure. Dorsal decubitis position was given to patients with maximall abducted state of right arm and then investigation was carried on right lobe over intercostal spaces. Reliability of liver stiffness measurements (LSM) was assumed with ten valid observation with <0.3 median of observation or with median <7.1 kPa for LS. Simultaneously CAP values were also obtained. CAP measurement of 248dB/m or above was assumed as hepatic steatosis. LS of ≥8 kPa was considered as liver fibrosis. Demographic and anthropometric data and laboratory tests, Biographic data, past history and clinical and laboratory details were recorded during the study.

Data was analyzed using SPSS version 26. Categorical variables were expressed as frequency and percentage. Numerical variables were presented as mean ± standard deviation if normally distributed otherwise were expressed as median with inter-quartile range (IQR). Numerical variables were compared among patients with and without fibrosis and steatosis using Mann-Whitney U test as they did not meet normality assumption. Spearman rank correlation was also determined among patients' features and steatosis and fibrosis. P-value less than or equal to 0.05 was taken as statistically significant.

RESULTS

Total 300 studied having mean age of 51.4±8.4 year while 161 (53.7) were females. Diabetes, hypertension and ischemic heart disease was present among 35%, 31.4% and 33.7% respectively. Mean value for anthropometry parameters including BMI, WC, HC, NC and WHR was 30.5 ± 3.5 Kg/m^2, 103.7 ± 10.8 cm, 107.9 ± 10.5 cm, 43.5 ± 3.4 cm, 51.4 ± 8.4cm, 0.9 ± 0.1 respectively. Median value for clinical biomarkers

including hemoglobin, TLC, platelets, HbA1c, triglycerides, creatinine, LDL, total bilirubin, ALT, AST, ALP, GGT, RBS, HDL, serum cholesterol was 11.5 (IQR=10.7-13.4), 8.8 (IQR=7.5-9.8), 300 (IQR=250-330), 6.7 (IQR=5.3-7.9), 130 (IQR=115-145), 1 (IQR=0.8-1.2), 120 (IQR=115-133.3), 1 (IQR=0.7-1.5), 0.7 (IQR=0.6-1), 50 (IQR=38-70), 37 (IQR=30-40), 87.5 (IQR=70-100), 35 (IQR=28-39), 150 (IQR=118-200), 180 (IQR=165-230), 39 (IQR=30-42). Mean CAP was 251 (IQR=219-342). Steatosis was present among 77.7% patients. Mean LS was 8.5 ± 8.2 kPa. Fibrosis was present among 76.3% patients. Table-I displays comparison of patients' demographic, anthropoemtery and clinical profile among those with and without steatosis. Age, WC, NC, HC, triglycerides, hemoglobin, creatinine, LDL, HDL, cholesterol, ALT, ALP and GGT were significantly different among patients with and without steatosis, Among patients with and without fibrosis, age, WC, WHR, NC HC, hemoglobin, creatinine, triglycerides, LDL, HDL, total bilirubin, serum cholesterol, ALT and ALP were significantly different (Table-I).

BMI: Body mass index, TLC: Total leukocyte count, RBS: Random blood sugar, LDL: Low density lipoprotein, HDL: High density lipoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: gamma-glutamyl transferase, *Significant at $p<0.05$, **Significant at $p<0.01$

Table-II displays correlation of patients' features and with CAP and fibrosis. Age, WC, NC, HC, triglycerides, LDL, HDL, ALT, ALP and cholesterol were significantly correlated with both steatosis and fibrosis. Creatnine and AST was correlated with steatosis only and total bilirubin was correlated with fibrosis only.

Variables	Steatosis Present Median (IQR)	Steatosis Absent Median (IQR)	P-Value	Fibrosis Present Median (IQR)	Fibrosis Absent Median (IQR)	P-Value
Age (years)	52.3±8.6	49.8±8.0	*0.017	52.4±8.5	48.4±7.7	**<0.001
BMI Kg/m^2)	30.8±3.6	30.1±3.3	0.083	30.5±3.5	30.7±3.7	0.584
Waist circumference (cm)	105.3±7.9	101.1±9.0	**<0.001	106.7±7.3	94.6±5.0	**<0.001
Neck circumference (cm)	43.8±2.8	42.8±4.1	**0.009	44.3±3.2	41.1±2.5	**<0.001
Hip circumference (cm)	109.8±8.5	105.3±9.4	**<0.001	111.1±7.9	99.2±5.7	**<0.001
Waist to hip ratio (cm)	0.95±0.1	0.96±0.1	0.710	0.96±0.2	0.95±0.1	**0.004
Hemoglobin (g/dl)	11.6±1.5	12.1±1.5	*0.020	11.7±1.5	12.4±1.4	**0.001
TLC (mm)	8.5±1.6	8.7±1.4	0.307	8.5±1.6	8.6±1.3	0.958
Platelets (10^9/L)	301.9±67.5	294.5±65.3	0.357	295.3±68.3	311.4±60.6	0.071
Creatinine (mg/dL)	1.1±0.3	0.9±0.4	*0.001	1.1±0.3	0.9±0.4	**0.007
RBS (mg/dl)	169.4±63.7	162.5±52.9	0.317	166.2±61.3	168.9±56.4	0.723
HbA1c (mmol/mol)	6.7±1.4	6.7±1.4	0.996	6.7±1.4	6.5±1.4	0.438
Triglycerides (mg/dL)	139.8±30.1	127.8±27.4	**0.001	140.0±32.3	121.8±11.8	**<0.001
LDL (mg/dL)	127.4±19.9	121.0±14.7	**0.002	127.1±19.8	119.2±11.9	**<0.001
HDL (mg/dL)	38 (30-41)	40 (32-42)	*0.050	36.1±7.5	38.4±8.9	*0.032
Serum cholesterol (mg/dL)	206.9±61.3	183.8±43.2	**0.001	202.1±59.6	188.2±44.6	*0.035
Total bilirubin (mg/dL)	1.1±0.6	1.2±1.2	0.761	1.2±0.8	1.1±1.1	0.220
ALT (IU/L)	55.2±19.5	47.4±15.5	**<0.001	54.6±18.8	45.1±15.5	**<0.001
AST (U/L)	39.8±14.9	36.1±8.6	*0.008	38.6±14.0	37.9±10.1	0.694
ALP (IU/L)	89.1±26.8	76.3±37.9	**0.001	86.7±26.1	78.0±44.6	*0.042
GGT (U/L)	39.2±18.3	34.1±15.5	*0.014	38.5±18.4	34.0±13.7	0.058

Table-I. Comparison of patients' features with steatosis and fibrosis presence

Variables	CAP	P-Value	Fibrosis	P-Value
Age (years)	0.156	**0.007	0.208	**<0.001
BMI Kg/m^2)	0.081	0.164	-0.042	0.467
Waist circumference (cm)	0.305	**<0.001	0.588	**<0.001
Neck circumference (cm)	0.305	**<0.001	0.520	**<0.001
Hip circumference (cm)	0.318	**<0.001	0.587	**<0.001
Waist to hip ratio (cm)	-0.037	0.526	-0.003	0.957
Hemoglobin (g/dl)	-0.803	0.150	-0.092	0.111
TLC (mm)	-0.082	0.156	-0.063	0.273
Platelets (10^9/L)	0.015	0.795	-0.104	0.073
HbA1c (mmol/mol)	0.047	0.421	0.069	0.235
Triglycerides (mg/dL)	0.134	*0.020	0.264	**<0.001
Creatinine (mg/dL)	0.148	*0.010	0.062	0.285
LDL (mg/dL)	0.186	**0.001	0.366	**<0.001
HDL (mg/dL)	-0.131	*0.024	-0.229	**<0.001
Total bilirubin (mg/dL)	0.069	0.231	0.208	**<0.001
ALT (IU/L)	0.200	**<0.001	0.155	**0.007
AST (U/L)	0.149	*0.010	-0.071	0.218
ALP (IU/L)	0.333	**<0.001	0.247	**<0.001
GGT (U/L)	0.248	**<0.001	0.120	*0.038
RBS (mg/dl)	0.045	0.440	-0.010	0.865
Serum cholesterol (mg/dL)	0.144	*0.013	0.210	**<0.001

Table-II. Correlation of anthropometry parameters and clinical biomarkers with steatosis and fibrosis

BMI: Body mass index, TLC: Total leukocyte count, RBS: Random blood sugar, LDL: Low density lipoprotein, HDL: High density lipoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: gamma-glutamyl transferase *Significant at $p<0.05$, **Significant at $p<0.01$

DISCUSSION

Age and the existence of steatosis and fibrosis are independently correlated, according to the analysis of the current study. There was no correlation found of BMI with steatosis and fibrosis. This finding supports a better correlation of visceral fat with NAFLD rather than overall increase in BMI. It also explains NAFLD existence in lean people. However, markers of central obesity including WC and HC found to be higher among steatosis and fibrosis. WC and HC had weak correlation with steatosis but with fibrosis they showed a medium positive correlation with fibrosis. In agreement to our study, Ni et al[12] also found a strong correlation of WC with liver fat. Clinically, a higher visceral-to-subcutaneous fat ratio has been seen in association with amplified risk for NAFLD progress and subsequent fibrosis.[13] The specific pathways involved in the pathophysiology of lean NAFLD are yet not properly discovered but a number of studies debate about the role played by cytokines.[14] One study found decreased levels of adiponectin among both lean NAFLD and obesity-related NAFLD.[15] To understand the cytokines function of cytokines lean NAFLD, more study is necessary.

Neck circumference was found to be correlated with the outcome variables and the literature supports that neck circumference is a marker of visceral fat, and positively correlates with the presence of steatosis and fibrosis.[16,17] This finding can be explained by the similarities between the selected population being Asian in origin, and ultrasound utilization for the detection of liver steatosis and fibrosis. No relationship was seen between WHR and steaosis or fibrosis. This is somewhat in contrast to the findings reported by another study which show a positive correlation between increasing waist to hip ratio and presence of steatosis and fibrosis.[18]

Another important finding was no association of platelets with steatosis and fibrosis. This is a

controversial observation, nevertheless, positive association between NAFLD and platelet count has been shown in studies carried out by Sung et al and Garjani et al.[19,20] Our research revealed a positive relationship between steatosis and fibrosis presence and serum creatinine (SCr). This is supported by other studies as well.[21,22] The results of other studies depict an independent relationship between increasing SCr (even within normal limits) and increased prevalence of steatosis and fibrosis.[21] Serum creatinine is a renal marker, and its association with liver injury leading to liver fibrosis is a promising future study aspect. Glycated hemoglobin (HbA1c) was found to be positively associated with hepatic fibrosis. This is aligned with another cohort study performed among the Asian population which showed a positive relation with the development of NAFLD with increasing HbA1c, and poor resolution of NAFLD in both diabetic and non-diabetic population.[23] This seems plausible in the light of insulin resistance and NAFLD as discussed above.[24]

There are certain limitations and strengths of the study. One important limitation is the inability to establish a causal relationship between the several factors, which is a limitation of the study-design. Second, a larger sample size and a more diversified population could reinforce the study's conclusions. Strength of the study includes the novelty of the idea, and further scope of research in this area. NAFLD is largely a silent disease, which can remain benign but may result in widespread complications ranging from cirrhosis to hepatocellular carcinoma.

CONCLUSION

Considerable interplay of metabolic factors, and anthropometric measures exist with NAFLD. It is important to monitor visceral fat measurements in the clinical practice, and screen for steatosis and fibrosis among the population with anthropometric and biochemical abnormalities. Early diagnosis of NAFLD can prevent further complications and disease progression by lifestyle changes, and stringent control of metabolic factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Punhal Khan	Conceptualized the study, Involved in data collection, Initial manuscript writing.	
2	Shahid Karim	Designed the study protocol, Critically revised the initial manuscript writing.	
3	Rajesh Kumar	Data collection, Initial manuscript writing.	
4	Vishal Kumar	Performed data analysis and involved in result writing.	
5	Afsheen Faryal	Performed data analysis and involved in result writing.