Research Article

Metabolic Dysfunction - Associated Fatty Liver Disease (MAFLD), and Lipid-Based Insulin Resistance Markers in Hepatitis C Virus Infection (HCV)

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Keywords

Insulin Resistance. Fatty Liver, Hepatitis C, Metabolic Syndrome, Liver Fibrosis, Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD), Lipid Profile

Abstract

Aim: Hepatitis C Virus (HCV) infection promotes insulin resistance, and metabolic dysfunction-associated fatty liver disease (MAFLD). HCV per se leads to impairment in host lipid metabolism and causes a deranged lipid profile. This study aims to analyze the prevalence of MAFLD and determine the levels of lipid profile parameters, surrogate markers of insulin resistance, liver fibrosis, and steatosis in patients with HCV infection.

Methods: This study used data from the Centers for Disease Control – National Health and Nutritional Examination Survey (CDC-NHANES) 2017-2020. Those who tested positive on HCV RNA PCR were included in HCV group (n=89). Propensity score-based age- and gender-matching was done among those tested negative for HCV to select controls (n=89). Homeostatic Model Assessment of Insulin Resistance (HOMAIR), Homeostatic Model Assessment of Beta-cell Function (HOMAB), and the lipid-based insulin resistance markers such as Visceral Adiposity Index (VAI), Lipid Accumulation Product (LAP), Triglyceride-Glucose Index (TyG) were calculated using the standard formulae.

Results: Serum triglycerides, total cholesterol and low-density lipoprotein cholesterol were significantly lower in HCV. HOMAIR, HOMAB were similar, and the lipid-based insulin resistance markers such as VAI, LAP and TyG index were significantly lower in HCV. FibroScan showed less steatosis, but increased fibrosis in the HCV patients. The surrogate markers of insulin resistance showed a significant association with the presence of MAFLD.

Conclusion: HCV patients showed hypocholesterolemia, hypotriglyceridemia and the levels of lipid-based insulin resistance markers were significantly lower. TyG index showed a strong positive association with the presence of MAFLD. These observations could be due to association between HCV replication and host lipid metabolism.

Introduction

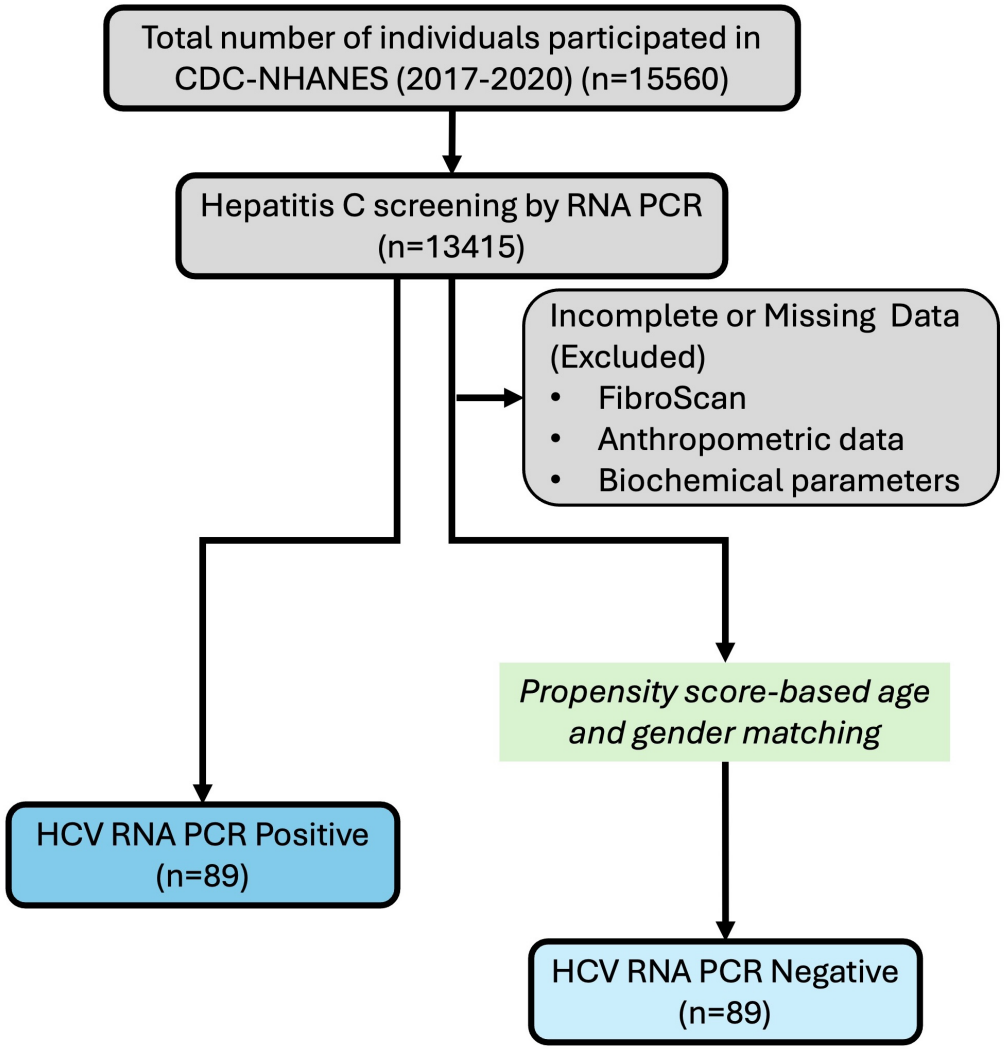
Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease, with global estimates indicating that around 50 million people have chronic HCV infection [1]. The prevalence of HCV is 0.5% in India, affecting 4.7 to 10.9 million people [2], with 54-86% of the infected population progressing to chronic HCV infection [3]. Persistent chronic inflammation caused by HCV predisposes to insulin resistance, especially in non-diabetic and non-obese patients, suggesting that HCV per se can induce insulin resistance [4]. HCV has been demonstrated to downregulate the hepatic expression of peroxisome proliferator-activated receptor – alpha (PPAR-α), a nuclear receptor mainly involved in regulating the genes encoding for enzymes of peroxisomal, microsomal, and mitochondrial β oxidation of fatty acids [5]. PPAR-α is known to regulate the import of fatty acids into the mitochondria by modulating the expression of carnitine palmitoyl transferase 1A (CPT1A), a crucial enzyme necessary for mitochondrial beta-oxidation [5]. HCV is also shown to activate the expression of sterol regulatory element-binding protein (SREBP)-1c, a transcription factor that controls fatty acid synthase, an enzyme responsible for lipid synthesis in the endoplasmic reticulum [6,7]. These observations suggest that HCV causes derangement of fatty acid metabolism, leading to the release of free fatty acids, promoting the formation of triacylglycerol in the liver, which results in steatosis. HCV is also reported to cause dyslipidemia, as it perturbs the metabolism of lipoproteins. HCV particles physically associate with liver-derived lipoproteins like very low-density and low-density lipoproteins (VLDL and LDL) to form highly infective lipo-viro particles (LVPs). Formation of LVPs confers protection to the virus against antibody-mediated immunity, thereby enhancing its infectivity [8] and replication in the liver. This also causes a reduction in LDL and VLDL levels in chronic HCV infection [9]. However, despite this reduction in atherogenic lipoproteins, the risk of insulin resistance, hepatic steatosis, and hepatic fibrosis persists.

Hepatic steatosis is commonly encountered in chronic HCV infection, as it is observed in nearly half of the patients [10], in which genotype 3a was predominant. In India, the prevalence of hepatic steatosis is 55.54% in patients with HCV infection, with genotype 3 being predominant (40-80%) [11]. Hepatic steatosis induces insulin resistance, which predisposes them to MAFLD. HCV is also reported to cause impairment of the insulin receptor substrate (IRS)-PI3 kinase signaling pathway, leading to insulin resistance [12]. HCV patients with concomitant MAFLD have poor clinical outcomes, as there is an increased risk of liver fibrosis [13]. The new definition for MAFLD as per the International Consensus Statement includes hepatic steatosis (determined by elastography or histology or biomarker-based fatty liver index) as a major criterion [14]. The studies employing this latest diagnostic criteria for MAFLD are limited. Hence, this study was done in an attempt to analyze the levels of lipid profile parameters, markers of insulin resistance, and the presence of MAFLD, liver steatosis, and fibrosis in patients with HCV infection.

Materials and Methods

This study was done using the Centers for Disease Control and Prevention – National Health and Nutritional Examination Survey (CDC-NHANES-2017-2020) data available in the public domain [15]. Informed consent was obtained from all the participants. Those who tested positive for HCV RNA by PCR were included in the HCV group (n=89). Propensity score-based age- and gender-matching was done among those tested negative for HCV RNA PCR to select age- and gender-matched controls (n=89) (Figure 1).

Figure 1: Flow chart depicting the screening and selection of participants from the survey data.



The chart describes the screening and selection of participants from CDC-NHANES survey data. Participants who tested positive for HCV RNA by PCR were included in the HCV group (n=89). Propensity score-based age and gender matching was done among those tested negative for HCV RNA PCR to select age- and gender-matched controls (n=89)

The participants were categorized as prediabetic or diabetic based on the HbA1c and fasting plasma glucose levels, using the American Diabetes Association criteria [16]. FibroScan-derived Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM) were used as markers of liver steatosis and fibrosis, respectively [17].

Homeostatic Model Assessment of Insulin Resistance (HOMAIR), Homeostatic Model Assessment of Beta-cell Function (HOMAB) were calculated using fasting plasma glucose and insulin values [18]. Using lipid profile and anthropometric measures, we calculated the Lipid Accumulation Product (LAP) [19], Visceral Adiposity Index (VAI) [20] and Triglyceride-Glucose Index (TyG) [21].

Statistical Analysis

All statistical analyses were done using R software version 4.3.1. The continuous data were represented as median and interquartile range. The distribution of the data was analyzed by Kolmogorov-Smirnov/Shapiro-Wilk test. The normally distributed data were compared using Independent t-test and non-normally distributed data were compared using Mann Whitney U test. Pearson's Chi-Square test was done to compare the categorical variables. Multivariate logistic regression was carried out to determine the association of covariates with the presence of MAFLD in a model adjusted for age and gender. The odds ratio (OR) was estimated by exponentiating the regression estimate. A p value of < 0.05 was considered statistically significant.

Criteria for diagnosis of Metabolic Syndrome and MAFLD

The guidelines proposed by American Heart Association-National Heart Lung Blood Institute (AHA-NHLBI) [22] and international expert consensus statement [14] were used for the diagnosis of metabolic syndrome and MAFLD respectively. These criteria were multiple and comprehensive and varies with gender, race, BMI and applying these manually is prone to error and misclassification. Hence, the standard R packages such as "MetabolicSyndrome" [23] and "MAFLD" [24] which employs the above mentioned criteria were used to establish accurate diagnosis in this study.

Results

Age and gender distribution were similar between the two groups, as controls were matched for age and gender using propensity score. The prevalence of diabetes was significantly lower in HCV group compared to controls (n (%), 7(8%) vs. 20(22%)); however, there was no difference regarding the presence of prediabetes. The proportion of participants with metabolic syndrome was similar between control and HCV groups (n (%), 33(37%) vs. 31(35%)). Presence of MAFLD were similar between HCV and controls (n (%), 25(60%) vs 39(71%)). Genotype 1 (n (%), 64(72%) was predominant among the HCV patients (Table 1).

Table 1: Baseline characteristics of participants of the study.

Parameter	Control (n=89)	Hepatitis-C (n=89)	p value
Age in years	60 (51-65)	60 (51-65)	1
Gender (male/female), n(%)	64/25 (72/28)	64/25 (72/28)	1
Diabetes/prediabetes, n (%)			<0.0001
Normoglycemia	26 (29)	41 (46)	
Prediabetes	41 (46)	41 (46)	
Diabetes Mellitus	20 (22)	7 (8)	
Metabolic syndrome, n (%)			0.87
Yes	33 (37)	31 (35)	
No	56 (63)	58 (65)	
MAFLD, n (%) #			0.333
Yes	39 (71)	25 (60)	
No	16 (29)	17 (40)	
HCV Genotype, n (%)			NA
Genotype 1	NA	64 (72)	
Genotype 2	NA	9 (11)	
Genotype 3	NA	10 (12)	
Genotype 4	NA	1 (1)	
Genotype 6	NA	1 (1)	
Genotype (undetermined)	-	2 (3)	

The baseline characteristics were compared between controls and those with Hepatitis-C infection. #MAFLD diagnosis was done in both the groups based on international expert consensus criteria [14]. Pearson's Chi-Square test was done to compare the difference in proportions of diabetes, metabolic syndrome and gender between two groups. $p < 0.05$ is considered statistically significant.

Hemoglobin and fasting plasma glucose levels were similar between the two groups. Liver function tests were deranged in HCV patients with significantly higher levels of globulins, AST, ALT, GGT, and total protein. Serum albumin levels were lower in patients with HCV. Serum ferritin levels were higher in patients with HCV; however, serum CRP levels were similar (Table 2).

Table 2: Hematological and Biochemical parameters.

Parameter	Control (n=89)	Hepatitis-C (n=89)	p value
Hematological parameters			
Hb, g/dL	14.1 (13.5-15)	14.6 (12.7-15.4)	0.87
Biochemical parameters			
Fasting plasma glucose, mg/dL	105 (101-114)	100 (93-115)	0.120
Total bilirubin, mg/dL	0.4 (0.3-0.6)	0.5 (0.3-0.62)	0.298
Total protein, g/dL	7.1 (6.9-7.3)	7.4 (7.2-7.8)	<0.0001
Albumin, g/dL	4 (3.8-4.3)	3.8 (3.6-4.1)	0.0002
Globulins, g/dL	3 (2.8-3.3)	3.6 (3.3-4.1)	<0.0001
Aspartate Transaminase (AST), IU/L	20 (17-25.5)	41 (29-66)	<0.0001
Alanine Transaminase (ALT), IU/L	19 (14.5-26.5)	41.5 (26-63.5)	<0.0001
Alkaline Phosphatase (ALP), IU/L	75 (65-89.5)	80 (67.5-96.8)	0.41
Gamma Glutamyl Transferase (GGT), IU/L	24 (17-42)	53.5 (28-141)	<0.0001
CRP, mg/L	1.74 (0.95-4.63)	1.67 (0.51-4.1)	0.171
Serum ferritin, ng/mL	138.5 (62.4-246.7)	184 (74-375)	0.051

The hematological and biochemical parameters were compared between controls and those with Hepatitis-C infection. Mann Whitney U test was done to compare the biochemical parameters between the two groups. $p < 0.05$ is considered statistically significant.

The HCV group had an improved lipid profile, with significantly lower serum total cholesterol (TC), triglycerides (TG), and LDL-C and VLDL-C compared to controls. (Table 3).

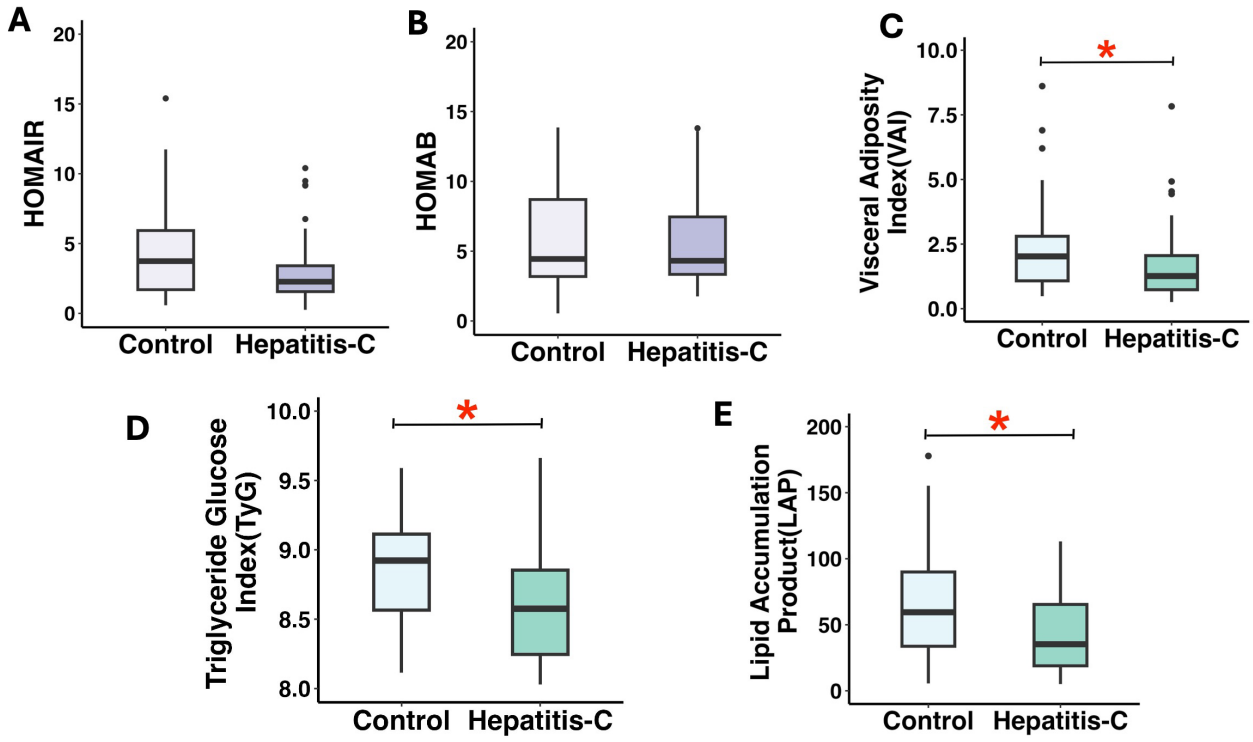
Table 3: Lipid profile parameters.

Parameter	Control (n=89)	Hepatitis-C (n=89)	p value
Lipid Profile			
Total cholesterol, mg/dL	190 (167-219)	162 (138-185)	<0.0001
Triglycerides, mg/dL	145 (99-193)	93 (71-124)	<0.0001
High-density lipoprotein cholesterol (HDL-C), mg/dL	48 (40-62)	50.5 (41-64)	0.368
Low-density lipoprotein cholesterol (LDL-C), mg/dL	117 (94-141)	92 (78-113)	0.01
Very low-density lipoprotein cholesterol (VLDL-C), mg/dL	24 (17-34)	15 (11-20)	<0.0001

The lipid profile parameters were compared between controls and those with Hepatitis-C infection. Mann Whitney U test was done to compare the lipid profile parameters between the two groups. $p<0.05$ is considered statistically significant.

The levels of HOMAIR, HOMAB were similar between the groups, (Figure 2A and 2B) and the lipid-based insulin resistance markers such as VAI, LAP and TyG index were significantly lower in the HCV group (Figure 2C-2E).

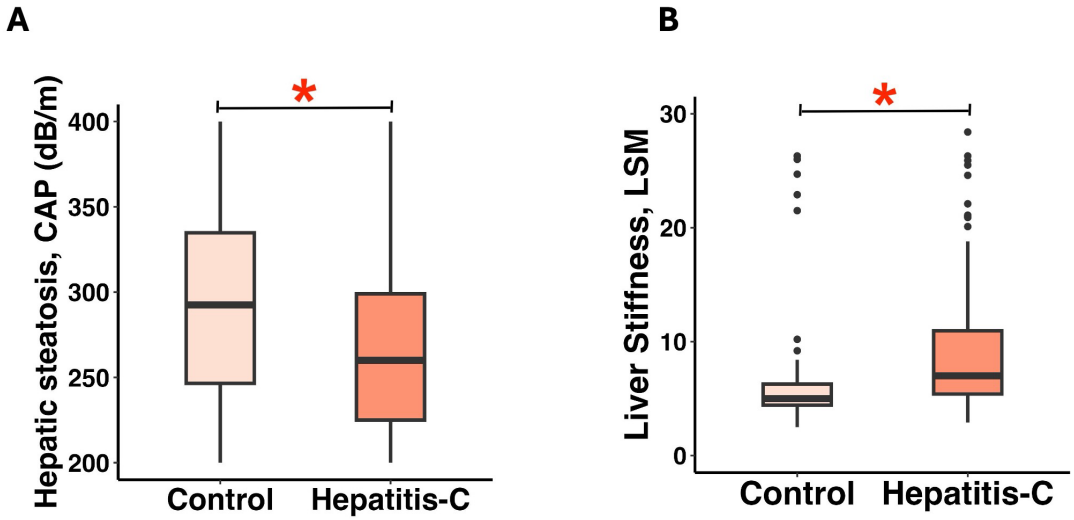
Figure 2: Markers of inuslin resistance.



Insulin resistance markers such as HOMAIR (2A), HOMAB (2B), VAI (2C), TyG (2D) and, LAP (2E) were compared between controls and those with Hepatitis-C infection. Mann Whitney U test was done to compare the insulin resistance markers between the two groups. *p < 0.05 is considered statistically significant.

Patients with HCV showed a significant decrease in liver steatosis (Figure 3A); however, liver stiffness (fibrosis) is increased (Figure 3B) compared to the control group.

Figure 3: Liver steatosis and fibrosis determined by elastography.



Controlled attenuation parameter (CAP in dB/m) and median liver stiffness (LSM in kPa) determined by elastography were used as markers for hepatic steatosis (3A) and fibrosis (3B). Mann Whitney U test was done to compare between the two groups. *p < 0.05 is considered statistically significant.

Using MAFLD status as the dependent variable, a multivariate logistic regression was done adjusting for age and gender. TyG index, VAI, LAP, HOMAIR, and HOMAB had a significant positive association with the presence of MAFLD. The odds ratio of TyG was 61.8, indicating its strong positive association with the presence of MAFLD (Table 4).

Table 4: Logistic regression to determine the association of covariates with the presence of MAFLD.

Parameter	Estimate	Odds ratio (adjusted)	p-value
HOMAIR	0.38	1.45	0.000807
HOMAB	0.08	1.08	0.0393
TyG index	4.13	61.8	0.0005
VAI	0.31	1.36	0.00619
LAP	0.018	1.02	0.000856
Serum Ferritin	0.0004	1.0004	0.696
Serum CRP	-0.01196	0.988	0.651

Logistic regression model adjusted for age and gender with MAFLD as the dependent variable. HOMAIR, HOMAB, VAI, TyG, LAP, serum ferritin and CRP were the covariates. *$p < 0.05$ is considered statistically significant.

Discussion

This study examined the metabolic alterations in those with HCV infection. HCV patients had lower levels of total cholesterol, triglyceride, and LDL (Table 3), suggesting a close link between HCV replication and host lipid metabolism. Similar findings have been reported previously in chronic HCV infection [9], and it was found that treatment with antivirals has shown improvement [25]. Despite the lipid-lowering effect observed in chronic HCV, cardiovascular disease is still higher compared to the HCV-negative individuals with higher TC and LDL levels [26]. The lipid-lowering effect is attributed to the fact that HCV replication in the liver alters the genes involved in fatty acid metabolism, promoting the synthesis of fatty acids and triacylglycerols [5–7].

In this study, patients with HCV infection showed significantly decreased liver steatosis compared to propensity-matched controls (Figure 3A). This could be because insulin resistance per se is a major determinant of liver fibrosis, irrespective of the genotype and extent of liver damage [27]. There are contrasting reports on genotype-specific effects on hepatic steatosis and fibrosis. In genotype 3, hepatic steatosis is related to viral load and hypolipidemia but not to fibrosis. However, in genotypes 1,2,4, insulin resistance and metabolic steatosis are associated with liver fibrosis [28]. This aligns with the observations of the current study, as genotype -1 was predominant (72%) and liver fibrosis was higher in HCV group.

Persistent chronic inflammation caused by HCV predisposes to insulin resistance, and studies have reported increased levels of HOMAIR in patients with HCV compared to controls [29]. However, in this study, HOMAIR and HOMAB were similar between groups. This could be because of the smaller sample size and missing data on fasting plasma insulin and glucose values. In addition, the proportion of people with diabetes is significantly lower in the HCV group compared to controls.

In this study, other surrogate markers of insulin resistance were studied, and it was found that VAI, LAP, and TyG were significantly lower in the HCV group. This could be attributed to the lipid-lowering effect of HCV, as evidenced by lowered levels of serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol.

Liver function tests were deranged in HCV group, indicating liver dysfunction. In the current study, serum ferritin levels were higher in HCV group but did not show any association with the presence of MAFLD. This is contrast to the studies that has shown increased ferritin levels are significantly associated with the presence of MAFLD [30,31]. This difference could be because of smaller sample size of the current study.

In this study, 60% of the HCV subjects had concomitant MAFLD diagnosed as per the International Consensus Statement [14]. HCV with concomitant MAFLD was shown to increase the risk of advanced liver fibrosis compared to controls [13]. It was found that markers of insulin resistance, such as HOMAIR, HOMAB, VAI, TyG, and LAP, showed a significant positive association with the presence of MAFLD. The odds ratio of TyG for MAFLD was high despite its levels being significantly lower in HCV group. Previous studies have reported that the TyG index was independently associated with liver steatosis and viral load in HCV genotype 1 patients. [32]. The LAP index was shown to be associated with steatosis in MAFLD [33]; however it utility in HCV with concomitant MAFLD has not been explored.

Limitations

The temporal relationship between HCV and lipid profile derangements could not be determined as this study was a cross-sectional study. Therefore, further large-scale cohort and mechanistic research is required to establish the role of HCV in MAFLD.

Conclusion

Patients with HCV presented with hypolipidemia and increased liver fibrosis. Routinely used inuslin resistance markers such as HOMAIR and HOMAB levels did not differ between groups; however, lipid-based insulin resistance markers, such as VAI, TyG, and LAP, were significantly lower in HCV patients. TyG index showed a strong positive association with the presence of MAFLD.

Statements and Declarations

Ethics Approval

The survey is approved by National Center for Health Statistics (NCHS) Ethics Review Board (ERB) (Protocol #2018-01, Continuation of Protocol #2011-17, effective through October 26, 2017). Informed consent was obtained from all participants.

Conflict of interests

The author does not have any conflict of interest to declare in this study.

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Data availability

This data is in the public domain and is available online.

Author contributions

JR was involved in data retrieval, acquisition, analysis and interpretation of the data, and wrote the manuscript. GB, AD and VM contributed to analysis and interpretation of data. MM was involved in data, analysis and interpretation of the data, and wrote the manuscript. JR conceptualized and designed the study, supervised the study in its entirety, analysed and interpreted the data, and wrote the manuscript. All authors reviewed the manuscript and approved its final version, and agree to be accountable for all aspects of the work in ensuring its accuracy and integrity.

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