https://doi.org/10.46389/rjd-2022-1026
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 4, pages 444-450

Original Article

Using chemerin and vaspin as non-invasive methods in diagnosing and monitoring chronic hepatitis C infection

Amina Hamed Ahmed Alobaidi [1]*, Sanarya Kamal Tawfiq [2], Staar Mohammed Qader [2]

[1] Department of Biochemistry and Pharmacology, College of Veterinary Medicine, University of Kirkuk, Kirkuk, Iraq
[2] Department of Microbiology, College of Medical Technology, AL-Kitab University, Kirkuk, Iraq

* Correspondence to: Amina Hamed Ahmed Alobaidi, Department of Biochemistry and Pharmacology, College of Veterinary Medicine, University of Kirkuk, Kirkuk, Iraq. Phone: +9647702399175; E-mail: minahamed2007@uokirkuk.edu.iq

Received: 30 July 2021 / Accepted: 16 August 2022

Abstract

Hepatitis C virus infection represents a healthcare problem in Iraq and worldwide. Early infection diagnosis ameliorates the disease's natural course and reduces morbidity and mortality. The study aimed to illustrate the connection between chemerin and vaspin in incessant hepatitis C disease. A cross-sectional investigation was completed in Kirkuk city from January to May 2019, which included 50 patients with chronic hepatitis C infection and 30 age and gender-matched controls. As a result, patients with chronic HCV had significantly ($P<0.05$) higher mean serum levels of chemerin than controls. In contrast, the mean serum level of vaspin was significantly ($P<0.05$) lower in patients with chronic HCV infection compared to controls. Chemerin's mean serum level was higher in grade 4 liver cirrhosis, while the lowest level was in those without cirrhosis (grade 0). However, the mean serum vaspin level increased with the grading of cirrhosis but declined in grade 4 to a level lower than that of stage 1. ($P<0.05$). Alanine aminotransferase transaminase serum levels were positively correlated with chemerin and vaspin serum levels. In conclusion, chemerin and vaspin serum levels may be used to monitor and predict stage liver fibrosis in chronic HCV.

Keywords: CHCV, chemerin, vaspin, fibrosis, HCV.

Introduction

Viral hepatitis is an infectious disease caused by viruses such as hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and hepatitis E virus [1]. HBV and HCV were characterized by the induction of chronic infection, more predominant in Asia and Africa and developed in the majority of infected cases [2], with subsequent liver cirrhosis or liver cancer [3]. Chronic HCV infection was asymptomatic until liver damage reached a level contributing to symptom production [3].

Chronic infection is the disease status in which HCV markers are detected for a period of >6 months [4]. Human HCV infection has a worldwide prevalence of about 3%, ranging from 0.5% to 2.3% and is pandemic [2, 5]. Human HCV infection is cleared spontaneously in about one-third of cases, while 15 to 30% of the other 2/3 developed chronic infections with subsequent liver cirrhosis and/or hepatocellular carcinoma [5]. The majority of human HCV is asymptomatic [6] and may form the focus for community transmission of the disease, hurdle its control, and increase the incidence and prevalence of HCV infection. Even though the impact of infection targets the liver, the infection may affect other organs [4]. At the point when fibrosis advances to cirrhosis, there is an extraordinary danger of multiple bad prognostic clinical statuses such as liver carcinoma and increased mortality [6]. Accordingly, it is imperative to screen perpetual liver infection to recognize its movement, start explicit medications, and choose whether progressively intrusive estimates like liver transplantation are required or not. Although the most widely recognized and predictive strategy for diagnosing and following liver fibrosis, biopsy is an obtrusive procedure with possible mistakes during the testing

procedure [7]. For a long time, liver biopsy has been viewed as the highest quality level for organizing liver fibrosis. Histological assessment likewise gives data on necroinflammatory action and different highlights, for example, steatosis and iron over-burden. A few scoring frameworks have been built up, the most widely recognized being the Ishak scoring, METAVIR, the Batts-Ludwig, Scheuer's, and the International Association for the Study of the Liver (IASL) frameworks [4].

Notwithstanding, other than its preferences, liver biopsy is an intrusive method with related dreariness. Minor confusions are generally normal and around 1/4 of patients have torment in the right shoulder or upper quadrant after liver biopsy [5]. Serious complexities are inconsistent, with special drainage rates ranging from 0.05% to 5.3% and mortality under 0.15% in the largest studies [7]. Chemerin is a newfound adipokine hormone that is fundamentally communicated by the liver and fat tissue and emitted in an inert structure as prochemerin and enacted by provocative and coagulation serine proteases [8]. Chemerin's demeanor is present in the lungs, liver and pancreas tissues. It has been demonstrated that chemerin is correlated with plasma triacylglycerol (TAG), body mass index and circulatory strain [9].

Vaspin is an instinctive fat tissue, an adipokine and serpin subsidiary, displaying a homology rate of 40% with alpha1-antitrypsin [10]. Vaspin is an adipokine isolated from subcutaneous and visceral adipose tissue [11]. The research documented that chronic hepatitis C virus infection is a metabolic disease thus, vaspin may play a potential role in CHCV pathogenesis [12]. Vaspin expression in the subcutaneous tissue correlates to body fat percentage [12], influencing the liver and skeletal muscle fatty tissue [8]. Along these lines, the point of the investigation was to explain the connection of chemerin and vaspin with viral heap of HCV in interminable hepatitis patients.

Material and methods

A cross-sectional study was completed in Kirkuk city from January to May 2019. The study included 50 endless hepatitis C-infected subjects. Their age range was 25–65 years of age — the cases were recruited from Hepatology and Gastroenterology Centre, Kirkuk. A control group included 30 apparently healthy subjects recruited from those who attended to Blood Bank for blood donation. The fibrosis stage was extracted from the patients' file document in HGC with confirmation from the specialist clinician. Venous five ml of fasting blood was gathered from all patients and controls at the examination time. Blood was left for clump and centrifuged 2 times for sera collection, which was then placed in Eppendorf tubes for later use to estimate chemerin, vaspin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total serum bilirubin (TSB). Chemerin and vaspin serum levels were determined using an Enzyme-Linked Immunosorbent Assay (ELISA), while ALT, AST, ALP and TSB were estimated using conventional biochemical tests.

Statistical analysis

Statistical analysis was performed using the SPSS package (version 24.1). Student t-test was used for mean comparison between patients and controls group. At the same time, the ANOVA test (One-way) was used to determine the significance of differences in relation to fibrosis stages. P-value of <0.05 was regarded as significant.

Results

The mean serum chemerin value was significantly (P<0.001) higher in CHC patients (20.08±9.7 ng/ml) as compared to controls (4.59±1.43 ng/ml) (Table 1). Additionally, the mean serum value of chemerin in chronic hepatitis C infection demonstrated an increasing trend with the increase of fibrosis stage. The mean chemerin serum value lowest (6.87±0.77 ng/ml) was in patients without fibrosis, while the highest level (32.04±2.44 ng/ml) was in those with stage 4 fibrosis (Table 2).

Vaspin mean serum level was significantly lower (P<0.05) in a patient with CHC (1.81±0.80 ng/ml) than that in the control group (2.22±1.02 ng/ml) (Table 1). In addition, vaspin mean serum value increased with the stage of fibrosis except for stage 4 (1.44±0.71 ng/ml), which is lower than that of stage 1 (1.53±0.24 ng/ml) value. However, the serum mean value in patients with stage 4 fibrosis was higher than that in patients without fibrosis (1.35±0.64 ng/ml). The differences in vaspin mean serum level between stages of fibrosis was highly significant (P<0.001) (Table 2).

The study showed that there was a highly significant (P<0.001) differences between patients with chronic hepatitis C and healthy control in mean serum values of ALT (patients=35.12±11.50 IU/ml; controls=13.01±4.43 IU/ml), AST (patients=28.1±9.16 IU/ml; controls=10.01±5.11 IU/ml), ALP

Table 1: Mean serum level of chemerin and vaspin in patients with chronic hepatitis C.

Variable		Patients (50)	Control (30)	t-value	P-value
Chemerin in ng/ml	Mean	20.08	4.59	8.668	<0.001
	SD	9.70	1.43		
Vaspin in ng/ml	Mean	1.81	2.22	1.999	<0.05
	SD	0.80	1.02		

Table 2: Chemerin and vaspin mean serum value in relation to fibrosis stages in patients with chronic hepatitis C.

Stages of fibrosis (number)	Chemerin in ng/ml		Vaspin in ng/ml	
	Mean	SD	Mean	SD
0 (8)	6.87	0.77	1.35	0.64
1 (11)	11.79	2.04	1.53	0.24
2 (11)	19.61	2.26	2.05	0.66
3 (9)	27.91	5.51	2.91	0.57
4 (11)	32.04	2.44	1.44	0.71
F	120.589		11.614	
P-value	<0.001		<0.001	

Note: 0 – No fibrosis; 1 – grade 1; 2 –grade 2; 3 – grade 3; 4 – cirrhosis.

(patients=199.01±43.13; controls=58.12±27.91 IU/ml and TSB (patients=7.12±2.01 mg/dl; controls=0.44±0.15 mg/dl) (Table 3).

The study showed a positive correlation of ALT with vaspin and chemerin in CHC patients (Figure 1), which means that chemerin and vaspin are elevated in chronic hepatitis C patients with elevation of ALT.

Discussion

Chronic diseases, in general, need monitoring and follow-up to achieve effective treatment outcomes and/or reduce morbidity and mortality. To date, the most accepted and regarded as a standard gold method for staging liver fibrosis is liver biopsy [13]. However, sampling and examiner-related variations influenced the findings and interpretation [14]. Hepatitis C chronic infection course warranted the need for selecting a predictive non-invasive tool for patient follow-up and monitoring. Previous studies suggested using novel adipokines to predict liver fibrosis staging [7, 11, 15, 16]. However, since chronic hepatitis C infection is considered a metabolic disease [17], and previous studies indicated that there were geographical variations in the prevalence of metabolic disorders [18]. Thus the

Table 3: Liver function tests (ALT, AST, ALP and TSB) in patients with chronic hepatitis C and the control group.

Variable		Patients	Control	t-value	P-value
ALT (IU/ml)	Mean	35.12	13.01	10.07	<0.001
	SD.	11.5	4.43		
AST(IU/ml)	Mean	28.1	10.01	9.86	<0.001
	SD.	9.16	5.11		
ALP(IU/ml)	Mean	199.01	58.12	15.50	<0.001
	SD.	43.13	27.91		
TSB(mg/dl)	Mean	7.12	0.44	18.12	<0.001
	SD.	2.01	0.15		

https://doi.org/10.46389/rjd-2022-1026

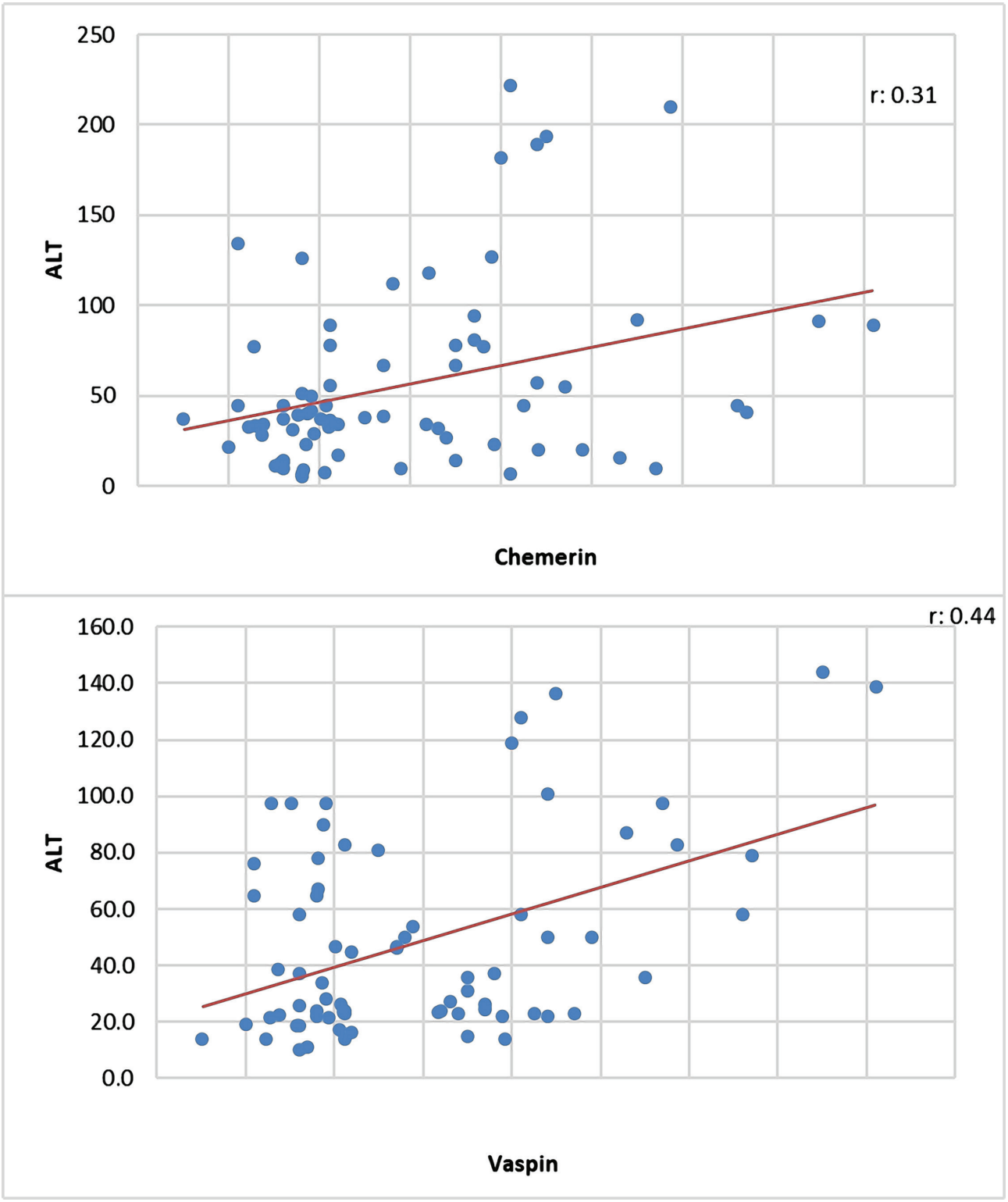

Figure 1: Correlation of ALT with chemerin and vaspin in CHC patients.

present study was performed to evaluate the predictive value of serum vaspin and chemerin in subjects with CHC in our community. Also, these biomarkers' determination can hypothetically offer an increasingly precise perspective on fibrogenic occasions happening in the whole liver with the benefit of giving a successive assessment of fibrosis without extra hazard [10].

The present study shows that the mean serum value of chemerin was significantly higher in CHC subjects compared to controls. In addition, the mean serum value increased with the increase in liver fibrosis staging. Also, this study demonstrated that the highest mean value of serum chemerin was detected among patients with endless hepatitis C who experienced cirrhosis

(grade 4) and the lowest mean value in those without fibrosis (grade 0). In contrast, the study indicated that the mean serum value of vaspin was significantly lower in patients than in controls. However, vaspin mean serum value increased with fibrosis staging increase but a decline in stage 4.

Previous studies reported that serum vaspin in subjects with CHC was lower than in controls, while serum chemerin was higher in patients [7]. Ali *et al.* [8] found that serum vaspin and chemerin serum levels were correlated with liver fibrosis staging, and mean serum value of vaspin was lower in chronic hepatitis C infection, while the chemerin value was higher than that in controls. Kukla *et al.* [7] reported that hepatic chemerin and Chemokine-Like Receptor 1 are expressed in chronic hepatitis C liver homogenate. Metabolic disturbances, staging of fibrosis, grade of steatosis and activity of necroinflammation were not demonstrating an association with chemokine-like receptors 1 and chemerin expression. In addition, there was an inverse correlation between chemerin expression and serum levels of chemerin. Thus chemerin may play a role in the pathogenesis and clinical outcome of chronic hepatitis C virus via induction of an increase in insulin sensitivity and transforming growth factor ß. Previous studies suggested that chemerin is shared in tissue inflammatory responses [19–21].

Serum vaspin diminished in patients with chronic hepatitis C infection and the vaspin levels were associated with steatosis grading [22]. However, vaspin detection in tissue and body fluids may potentially predict systemic inflammation [23]. The previous studies indicated that serum vaspin was decreased in subjects with CHC; however, the levels were positively associated with the increase in liver fibrosis [7, 8, 11, 22] and hepatocellular carcinoma [24]. This pattern may suggest that the vaspin increase was a compensatory mechanism as a defense process to suppress inflammatory responses. In CHC subjects, a positive correlation of vaspin with fasting glucose and the expression of vaspin mRNA induction in human body fat may confirm the compensatory mechanism of vaspin in obese individuals and with insulin resistance [7].

Rabe *et al.* [25] reported that TNF-α, leptin and resistin expression was suppressed by vaspin and contributed to the improvement of insulin resistance. Low vaspin levels in subjects with chronic hepatitis C viral infection may enhance inflammatory responses via overexpression of TNF-α and the development of insulin resistance, increasing disease severity and prognosis [7]. This study's finding indicated a significant increase in serum vaspin values in relation to the progression of liver fibrosis in agreement with previous studies; however, they did not agree with one report, which did not include cases with cirrhosis in their analysis [7, 8, 22].

Leptin demonstrates protection from fatty liver development; however, it enhances inflammation responses and acceleration of fibrosis [7]. Thus vaspin may induce its protective effect in chronic hepatitis C viral infection through the suppression of leptin. In addition, vaspin upregulation may play a role in liver fibrosis advancement in CHC.

The present study shows that subjects with CHC had a higher significant serum chemerin mean value than controls and the serum concentration increased with an increase in fibrosis grading. These findings corresponded with those reported by others [7, 8, 15]; however, Kukla *et al.* [7] found that low chemerin levels demonstrated in CHC with low inflammatory responses, while cases with severe to moderate inflammation show lower chemerin levels. The present study results and the previous reports indicate a role for chemerin in the pathogenesis of hepatitis C viral infection. Thus, patients with low chemerin may have high morbidity and mortality, a predictor of disease prognosis [7].

The association of low serum chemerin values with inflammation severity may be attributed to the binding of chemerin to inflammatory cells receptor and subsequent migration to the inflammation site and potentiate inflammatory responses and injury to hepatocytes [7]. Chemerin induces the activation of natural killer cells and promotes the antiviral activity of NK cells. In subjects with CHC stage of fibrosis unrelated to chemerin serum levels [7], their finding interpretation may be influenced by their study cohort, except those with cirrhosis. However, this study shows a significant association between fibrosis grade and serum chemerin levels in accordance with other studies [8].

Abdel-Messeih *et al.* [15] found a significantly higher serum chemerin in subjects with chronic hepatitis C virus infection than in controls and suggested that serum chemerin determination was a predictive value for prognosis monitoring instead of liver biopsy. ALT, AST, ALP and TSB were increased in our study cohort in a positive association pattern with the increase of serum chemerin, which agreed with the findings of others [7, 15, 26, 27]. These findings confirm the predictive role of serum chemerin estimation as a non-invasive biomarker for monitoring CHC prognosis.

Peschel *et al.* [16] reported a significant correlation between liver fibrosis measurement using fibrosis-4

 https://doi.org/10.46389/rjd-2022-1026

and a decrease in serum chemerin. In addition, they found that serum chemerin was inversely correlated with liver function tests in subjects with chronic hepatitis C infection. However, the present study shows positive correlation between serum chemerin values and ALT. Also, Shawkey *et al.* [28] found that liver fibrosis histological scores were increased with serum chemerin increasing. Chemerin serum levels decreasing in association with the increase of fibrosis staging may be restricted to those with advanced liver disease [16]. In serum chemerin, the interpretation must consider sample size, BMI, viral load, HCV genotype and gender [7, 16, 29–32].

The literature suggests that chronic hepatitis C infection is beyond hepatic disease involving inflammatory, immunological and metabolic abnormalities [7, 19, 33]. Chemerin acts as a chemoattractant for macrophages, dendritic cells (DC), NK cells activation, synthesis of TGF-ß, enhancement of monocytes, increase of nuclear factor-kB, increase in synthesis of interleukin 1ß, angiogenesis enhancement, increase of synthesis and activation of vascular endothelial growth factor, activation of mitogen-activated protein kinase and protein kinase B in endothelial cells and macrophage grip to vascular cell bond atom 1 (VCAM1) and fibronectin [7, 34, 35]. However, positive functions were demonstrated by chemerin in CHC, including decreased synthesis of IL-6, decrease in TNF-α production, IL-10 production stimulation, increased synthesis and activity of matrix metalloproteinases, improved insulin sensitivity, the reduced release of glucose from hepatocytes, and glucose uptake increase [7].

Hepatitis C chronic infection contributed to extrahepatic complications that include metabolic disturbances of lipid and glucose, atherosclerosis, iron metabolic pathway alteration, lymphoproliferative diseases, mixed cryoglobulinemia, insulin resistance, renal disease, type 2 diabetes (T2DM), autoimmune diseases, rheumatoid arthritis-like polyarthritis, sicca syndrome, and autoimmune diseases [33, 36, 37].

Although the current evidence of the performed studies indicated the potential effect of chemerin in CHC pathogenesis, further research is still needed to explore the causes of variations between studies and clarify its functions [9]. Chemerin limits the harmful effects of IL-6 and TNF-α by restraining their inflammatory effects and may apply a defensive mechanism against liver damage [34]. Antiviral treatment of HCV infection does not affect serum chemerin levels; thus, serum chemerin estimation may serve as a biomarker for liver injury pre- and post-treatment [19].

Conclusion

Serum vaspin was significantly lower, while chemerin levels were significantly higher in subjects with CHC infection than in controls and their serum values increased with liver fibrosis staging. Both biomarkers were significantly correlated with ALT. Serum mean values of ALT, AST, ALP and TSB were lower in controls than in CHC patients. Thus, the estimation of serum vaspin and chemerin was a predictive non-invasive tool for monitoring the mortality in cases of CHC.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

The study protocol was approved by the Kirkuk University College of Veterinary Medicine Ethical Committee and the Kirkuk Health Authority Ethical Committee.

Informed consent

Verbal informed consent was taken from each patient before their enrolment in the study.

References

1. Lanini S, Ustianowski A, Pisapia R, *et al.* Viral Hepatitis: Etiology, Epidemiology, Transmission, Diagnostics, Treatment, and Prevention. Infect Dis Clin North Am 33(4):1045-1062, 2019.
2. WHO. Hepatitis C 2020 www.who.int
3. Baumert TF, Jühling F, Ono A, *et al.* Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. BMC Med 15(1):52, 2017.
4. Barreiro P, Labarga P, Fernandez-Montero JV. Rate and indicators of serum HCV-RNA>6 million IU/mL in patients with ceaseless hepatitis C. Diary of Clinical Virology 71:63-66, 2015.
5. Alazzawy MA. Role of Interleukin-28B in clearance of HCV in acute and chronic hepatitis patients in Kirkuk city. Kurd J App Res 3(2):146-149, 2018.
6. Cheung M, Mutimer D, Agarwal K, *et al.* Long haul genuine line up of patients with unending hepatitis C infection and decompensated cirrhosis after direct acting antivirals– what is the clinical advantage of antiviral treatment? Diary Hepatol 68:109-110, 2018.
7. Ali S, Ellakwa D, Emara S, *et al.* The role of chemerin and vaspin in Egyptian patients with viral hepatitis C. Meta Gene 18:23–30, 2018.

8. Kaur J, Mattu HS, Chatha K, *et al*. Chemerin in human cardiovascular disease. Vascular Pharm 110:1–6, 2018.
9. Karajibani M, Montazerifar F, Bakhshipour A, *et al*. Serum omentin-1, vaspin, and apelin levels and central obesity in patients with nonalcoholic fatty liver disease. J Res Med Sci 22(1):70,2017.
10. Marei ES, Gaber HM, Shaheen DS. Potential role of vaspin and apelin in chronic hepatitis C virus patients with and without diabetes. J Rad Res Appli Sci 13(1):155-163, 2020.
11. Moschen AR, Kaser A, Enrich B, *et al*. Visfatin an adipokine with proinflammatory and immunomodulating properties. J Immunol 178:1748-1758, 2007.
12. Mendes LC, Stucchi RSB, Vigani AG. Diagnosis and staging of fibrosis in patients with chronic hepatitis C: Comparison and critical overview of current strategies. Hepatitis Medicine Evidence Res 10:13-22, 2018.
13. Oeda S, Tanaka K, Takahashi H. Diagnostic accuracy of fibroscan and factors affecting measurement. Diagnostics 10:940, 2020.
14. Kukla M, Adamek B, Waluga M, *et al*. Hepatic chemerin and chemokine-like receptor 1 expression in patients with chronic hepatitis C. BioMed Res Inter 5 :177-183, 2014.
15. Abdel-Messeih PL, Mansour HH, Ibrahim DR. Evaluation of chemerin and leptin in serum of chronic hepatitis C patients. J Histol Cell Biol 1(1):8-12, 2018.
16. Peschel G, Grimm J, Gülow K, *et al*. Chemerin Is a Valuable Biomarker in Patients with HCV Infection and Correlates with Liver Injury. Diagnostics (Basel) 10(11):974, 2020.
17. Kierepa, A., Witkowska, A., Kaczmarek, M. *et al*. Impact of chronic HCV treatment on quality of life of patients with metabolic disorders in context of immunological disturbances. Sci Rep 10:10388, 2020.
18. DeBoer MD, Filipp SL, Gurka MJ. Geographical variation in the prevalence of obesity and metabolic syndrome among US adolescents. Pediatr Obes 14(4):e12483, 2019.
19. Buechler C. Chemerin in Liver Diseases. Endocrinol Metab Syndrome 3: 144, 2014.
20. Yilmaz Y, Kurt R, Gurdal A, *et al*. Circulating vaspin levels and epicardial adipose tissue thickness are associated with impaired coronary flow reserve in patients with nonalcoholic fatty liver disease. Atherosclerosis 217(1):125-129, 2011.
21. Sell H, Divoux A, Poitou C, *et al*. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 95:2892-2896, 2010.
22. Ramadan RA. Serum vaspin and insulin resistance: predictors of steatosis and fibrosis in Egyptian patients with genotype 4 chronic hepatitis C. Advance Lab Med Inter 7:48–64, 2013.
23. Pradeep AR, Karvekar S, Nagpal K, *et al*. Vaspin: a new adipokine correlating the levels of crevicular fluid and tear fluid in periodontitis and obesity. J Invest Clin Dent 7(3):232–238, 2015.
24. Pazgan-Simon M, Kukla M, Zuwała-Jagiełło J, *et al*. Serum visfatin and vaspin levels in hepatocellular carcinoma (HCC). PLoS One 15(1):e0227459, 2020.
25. Rabe K, Lehrke M, Parhofer KG, *et al*. Adipokines and insulin resistance. Mol Med 14(11-12):741-751, 2008.
26. BashirMF, Haider MS, Rashid N, Riaz S. Association of biochemical markers, hepatitis C virus and diabetes mellitus in Pakistani males. Trop J Pharm Res 12(5):845-850, 2013.
27. Ibrahim D, Abdel-Messeih PL. Prognostic value of serum retinoic acid receptor responder protein 2 (RARRES2) in chronic hepatitis C patients. Med J Cairo Univer 88:1109-1115, 2020.
28. Shawkey A, Ellakwa D, Emara S, *et al*. The role of chemerin and vaspin in Egyptian patients with viral hepatitis C. Meta Gene 18:23–30, 2018.
29. Alfadda AA. Circulating Adipokines in Healthy versus Unhealthy Overweight and Obese Subjects. Int J Endocrinol 2014:170434, 2014.
30. Gu P, Jiang W, Lu B, Shi Z. Chemerin is associated with inflammatory markers and metabolic syndrome phenotypes in hypertension patients. Clin Exp Hypertens 36:326–332, 2014.
31. Marwa OED, Al-Aliaa MS. Chemerin is an indispensable pre-treatment predictor of sofosbuvir pegylated interferon-alpha and ribavirin outcomes in chronic hepatitis C Egyptian patients. Az J Pharm Sci 60:111–121, 2019.
32. Keikha M, Eslami M, Yousefi B, *et al*. HCV genotypes and their determinative role in hepatitis C treatment. Virus Dis 31:235–240, 2020.
33. Chaudhari R, Fouda S, Sainu A, *et al*. Metabolic complications of hepatitis C virus infection. World J Gastroenterol 27(13): 1267-1282, 2021.
34. Cash JL, Hart R, Russ A, *et al*. Synthetic chemerin-derived peptides suppress inflammation through ChemR23. J Exp Med 205(4):767-75, 2008.
35. Kaur J, Adya R, Tan BK, *et al*. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem Biophys Res Commun 391(4):1762-1768, 2010.
36. Fabrizi F, Donato FM, Messa P. Hepatitis C and Its Metabolic Complications in Kidney Disease. Ann Hepatol 16:851-861, 2017.
37. Younossi Z, Park H, Henry L, *et al*. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. Gastroenterology 150:1599-1608, 2016.

https://doi.org/10.46389/rjd-2022-1026