*Original Research Article*

# Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Antibodies Levels in Chronic Viral Hepatitis (B&C)


## Abstract:

**Background:** Extrahepatic manifestations is a relatively common feature in patients with chronic hepatitis C virus infection. Among the different clinical disorders associated with HCV infection, articular involvement is a frequent complication, and the clinical picture of HCV related arthropathy varies widely. In particular, monoarticular or oligoarticular involvement affects larger joints and is typically associated with mixed cryoglobulinemia, whereas symmetric polyarthritis associated with HCV infection frequently displays a rheumatoid arthritis like clinical picture which can be clinically indistinguishable from RA itself. This study aimed to evaluate level of Rheumatoid Factor and anti-CCP level in chronic viral hepatitis B&C.

**Patients and Methods:** Thirty patients with rheumatoid arthritis, thirty patients with chronic hepatitis C virus and thirty patients with chronic hepatitis B virus were selected to perform this study and they were compared to thirty normal subjects as a reference group.

**Results:** There was significant difference between the hemoglobin in the four groups. As regard Rheumatoid Factor there was significant difference between the studied groups. As regard Anti-CCP, there was significant difference between the studied groups. There was also significant difference between the four groups according to level of positivity. Finally, our study shows clinically significant positive correlation between RF as well as anti CCP titer and both HBV DNA and HCV RNA viral levels.

**Conclusions:** Rheumatoid factor was found with considerable percentage in chronic HBV & HCV patients without musculoskeletal manifestations. Anti-CCP can be detected with low positivity in chronic HBV&HCV patients even without arthritic manifestations. There is a significant positive correlation between RF titre and HBV DNA& HCV RNA in chronic hepatitis patients. There is a significant positive correlation between anti-CCP and HBV DNA& HCV RNA in chronic hepatitis patients. Chronic HBV & HCV can be considered and investigated in patients with positive RF and/or anti CCP without arthritic manifestations.



**Keywords:** Rheumatoid Factor, Anti-Cyclic Citrullinated Peptide Antibodies Levels, Chronic Viral Hepatitis

## Introduction:

Globally, around 400 million people live with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, with no country/region left unaffected; 1.4 million people die every year from complications of viral hepatitis. There is a lack of global awareness, and most persons with hepatitis remain undiagnosed. Yet most of these deaths can be prevented as there are highly effective measures to prevent new HBV and HCV infections and highly effective treatments that can suppress HBV replication and cure HCV infection. [(1)]

Chronic hepatitis C virus (HCV) infection is a public health problem, with about 71 million people infected worldwide. It is a leading cause of liver related morbidity and mortality through its predisposition to liver fibrosis, cirrhosis, and liver cancer. Each year, hepatitis C causes approximately 399,000 deaths worldwide, mostly from cirrhosis and hepatocellular carcinoma (HCC). [(2)]

In addition to hepatic diseases, HCV infection has also been found to be involved in a variety of extra-hepatic diseases, affecting the kidneys, skin, salivary glands, eyes, thyroid, joints, nervous system, and immune system. Extra-hepatic diseases are reported in up to three quarter of patients and produce an important burden for society and health care systems. [(3)]

Following the natural course of infection, 20–30% of infected patients develop liver cirrhosis within 20–30 years after infection. [(7)] Of these patients, 1–8% will develop hepatocellular carcinoma (HCC), and 67–91% will die due to liver-related causes. [(5)]

HCV infection causes approximately one-third of all HCC cases globally. [(6)]

Chronic hepatitis B virus (HBV) infection is a global public health problem, because persistent viremia is associated with increased morbidity and mortality. [(7)]

Approximately 240 million people are chronic HBV surface antigen (HBsAg) carriers, with large regional variations between low (<2%) and high (>8%) endemic areas. [(8)]

The number of HBV related deaths from cirrhosis and/or hepatocellular carcinoma (HCC) has significantly increased in the last 20 years and more than 500,000 people die every year. [(9)]

Anti-citrullinated protein antibodies (ACPA) and RF are autoantibodies present in the majority of rheumatoid arthritis patients. Among these, anti-cyclic citrullinated peptide (anti-CCP) antibodies are widely known to be an important diagnostic and prognostic tool due to their high specificity. [(10)]

Anti-CCP and RF are important indicators in RA diagnosis, but they can be positive for various infections and connective tissue diseases.[(11-15)]

This study aimed to evaluate level of Rheumatoid Factor and anti-CCP level in chronic viral hepatitis B&C.

## Subjects and Methods:

This study was carried out on 120 subjects divided into four groups:

**Group I:** 30 healthy individuals as control group.

**Group II:** 30 patients with chronic hepatitis B infection.

**Group III:** 30 patients with chronic hepatitis C infection.

**Group IV:** 30 patients with rheumatoid arthritis.

They are attendants of the Internal Medicine Department, Tanta University Hospital as well as El-Menshawy General Hospital. This study was carried out during the period from July 2018 to the end of August 2019. Approval for the study was taken from the ethical committee of faculty of medicine, Tanta University. Informed consent was obtained from all subjects after full explanation of benefits and risk.

### Inclusion criteria

1- Patients with chronic hepatitis B based on:

- Persistence of the hepatitis B surface antigen (HBsAg) for more than 6 months.

- Patients were determined to be carriers of inactive HBV (level of HBV DNA below 2000 IU/mL and serum levels of ALT that remained normal).

2- Patients with chronic hepatitis C infection (defined by the presence of anti-HCV and HCV-RNA positivity).

3- Patients with RA:

- Fulfill The ACR/EULAR 2010 classification criteria for rheumatoid arthritis.

**Exclusion criteria**

Hepatitis B or C Patients with already defined specific musculoskeletal symptoms or who have received antiviral therapy will be excluded from the study.

**All cases included in the study were subjected to the following:**

- Full history taking.
- Complete clinical examination.
- Abdominal ultrasonography.
- Laboratory investigations including:

**Routine laboratory investigations**

- Complete blood count.
- Liver function tests (AST, ALT, PT, Serum Albumin).
- Blood urea and serum creatinine.
- C-reactive protein (CRP).
- Erythrocyte sedimentation rate (ESR).
- Hepatitis B surface antigen (HBsAg).
- Anti hepatitis C antibody (anti-HCV).
- HCV-RNA by polymerase chain reaction (PCR).
- HBV DNA level.

**Specific investigations**

- Rheumatoid factor using enzyme-linked immunosorbent assay (ELISA).
- Anti cyclic citrullinated antibody (anti-CCP) using enzyme-linked immunosorbent assay (ELISA).

**Sample collection**

Use preferentially freshly collected serum samples. Blood withdrawal must follow national requirements. Do not use icteric, lipemic, hemolyzed or bacterially contaminated samples. Sera with particles should be cleared by low speed centrifugation (<1000 x g). Blood samples should be collected in clean, dry and empty tubes. After separation, the serum samples should be used during the first 8h, respectively stored tightly closed at 2-8°C/35-46°F up to 48h, or frozen at -20°C/-4°F for longer periods.

**Assay procedure**

**For rheumatoid factor:** Rapid latex agglutination test for qualitative screening of heumatoid factor (anti-gamma globulin in serum) done by biomed diagnostic.

**Statistical Methods**

Statistical analysis and presentation of data was conducted using Statistical Package for the Social Sciences version 22 computer program. Categorical data were presented as numbers and percentages. Chi-Square or Fisher's Exact tests as appropriate were applied to investigate the association between categorical variables. Data were expressed as mean ± standard deviation and One-Way ANOVA was used for comparison between the studied groups. When

ANOVA results were significant, post hoc Games-Howell test was applied for pairwise comparison between the groups.

## Results:

Table (1) show there was significant difference in Hb with significant lower Hb in HCV, HBV and RA groups in comparison to control group.

| | | Groups | | | | One-way ANOVA | |
|---|---|---|---|---|---|---|---|
| | | Control N=30 | Chronic Hepatitis B N=30 | Chronic Hepatitis C N=30 | Rheumatoid Arthritis N=30 | F | P value |
| Hb gm/dl | Range | 3.5 – 15.3 | 12.5 – 14 | 12 – 14.9 | 10.5 – 14.5 | 27.742 | 0.001* |
| | Mean | 14.58 ± 0.53 | 13.53 ± 0.39 | 13.82 ± 0.53 | 13.30 ± 0.79 | | |

Table (2) show demonstrated comparison between studied groups regarding RF. Group I: RF was negative in 100% of cases. Group II: RF was negative in 26 cases (86.7%) and positive in 4 cases (13.3%). Group III: RF was negative in 24 cases (80%) and positive in 6 cases (20%). Group IV: RF was negative in 6 cases (20%) and positive in 24 cases (80%). (p=<0.001*, X2=55.649). By comparison there was significant difference between the studied groups as regard Rheumatoid factor positivity.

**Table (2): Comparison of RF positivity in the studied groups**

| | | | Groups | | | | Chi-Square test | |
|---|---|---|---|---|---|---|---|---|
| | | | Control N=30 | Chronic Hepatitis B N=30 | Chronic Hepatitis C N=30 | Rheumatoid Arthritis N=30 | $X^2$ | P value |
| RF | Negative | N | 30 | 26 | 24 | 6 | 55.649 | <0.001* |
| | | % | 100% | 86.7% | 80% | 20% | | |
| | Positive | N | 0 | 4 | 6 | 24 | | |
| | | % | 0.0% | 13.3% | 20% | 80% | | |

*Significant at p<0.05.

Table (3) show Comparison of RF titre in the studied groups. Group I, control group RF ranges between (4– 7) U/ml with mean value of 5.17±0.79 U/ml. Group II, chronic hepatitis B group RF range was between (6– 64) U/ml with mean value of 9.3±10.9U/ml. Group III, chronic hepatitis C group RF range was between (5– 128) U/ml with mean value of 13.93±25.9U/ml. Group IV, rheumatoid arthritis group RF range was between (5– 512) U/ml with mean value of 114.8±164.2U/ml. (p=<.001*, F=12.042). By comparing the four groups there was significant difference in RF level in the studied groups with significant higher level in RA in comparison to other groups and significant higher level in HBV&HCV group in comparison to control group.

**Table (3): Comparison of RF titre in the studied groups**

| | | Groups | | | | One-way ANOVA | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Group I N=30 | Group II N=30 | Group III N=30 | Group IV N=30 | F | P value | Post Hoc Test | | | | |
| RF U/ml | Range | 4 – 7 | 6 – 64 | 5 – 128 | 5 – 512 | 12.042 | 0.001* | P1 | 0.848 | P4 | 0.830 | |
| | Mean | 5.17± 0.79 | 9.3± 10.9 | 13.93± 25.9 | 114.8± 164.2 | | | P2 | 0.684 | P5 | 0.001* | |
| | | | | | | | | P3 | 0.001* | P6 | 0.001* | |

P1: Group I versus Group II, P2: Group I versus Group III, P3= Group I versus Group IV, P4: Group II versus Group III, P5: Group II versus Group IV, P6: Group III versus Group IV

Table (4) show demonstrated comparison between studied groups regarding Anti-CCP level of positivity. Group I: Anti-CCP was negative in 100% of cases. Group II: Anti-CCP was negative in 27 cases (90%) and low positive in 3 cases (10 %). Group III: Anti-CCP was negative in 26 cases (86.7%) and low positive in 4 cases (13.3%). Group IV: Anti-CCP was negative in 7 cases (23.3 %), low positive in 6 cases (20%) and high positive in 17 cases (56.7 %). (p=<.001*, X2=62.78). By comparing the studied groups there was significant difference in anti-CCP positivity and level of positivity with significant higher positivity in Rheumatoid arthritis group in comparison to the other groups.

**Table (4): Comparison of Anti-CCP level of positivity in the studied groups**

| | | | Groups | | | | Fisher's Exact test | |
|---|---|---|---|---|---|---|---|---|
| | | | Group I N=30 | Group II N=30 | Group III N=30 | Group IV N=30 | $X^2$ | P value |
| Anti-CCP U/ML | Negative | N | 30 | 27 | 26 | 7 | 62.78 | <0.001* |
| | | % | 100.0% | 90.0% | 86.7% | 23.3% | | |
| | High positive | N | 0 | 0 | 0 | 17 | | |
| | | % | 0.0% | 0.0% | 0.0% | 56.7% | | |
| | low positive | N | 0 | 3 | 4 | 6 | | |
| | | % | 0.0% | 10.0% | 13.3% | 20.0% | | |

Table (5) show demonstrated comparison between four groups regarding Anti-CCP titre. Group I, control group Anti-CCP range was between (1.04–6.5) U/ml with mean value of 3.34±1.2 U/ml. Group II, chronic hepatitis B Anti-CCP range was between (0.39– 30) U/ml with mean value of 6.61±7.3 U/ml. Group III, chronic hepatitis C Anti-CCP range was between (1.37 – 33) U/ml with mean value of 7.14±8.8 U/ml. Group IV, rheumatoid arthritis group Anti-CCP ranges between (2.8 – 99.2) U/ml with mean value of 55.40±32.5U/ml. (F=55.795, p=0.001*) By comparing the four groups there was significant difference in anti-CCP value between the studied groups with significantly higher level in Rheumatoid arthritis group in comparison to chronic hepatitis B&C group and significantly higher level in both chronic hepatitis B&C groups in comparison to control group.

**Table (5): Comparison of Anti-CCP titre in the studied groups**

| | | Groups | | | | One-way ANOVA | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Group I N=30 | Group II N=30 | Group III N=30 | Group IV N=30 | F | P value | Post Hoc Test | | | | |
| Anti CCP | Range | 1.04 – 6.5 | 0.39 – 30 | 1.37 – 33 | 2.8 – 99.2 | 55.795 | 0.001* | P1 | 0.465 | P4 | 0.904 |
| | Mean | 3.34±1.2 | 6.61±7.3 | 7.14±8.8 | 55.40±32.5 | | | P2 | 0.394 | P5 | 0.001* |
| | | | | | | | | P3 | 0.001* | P6 | 0.001* |

1: Group I versus Group II, P2: Group I versus Group III, P3= Group I versus Group IV, P4: Group II versus Group III, P5: Group II versus Group IV, P6: Group III versus Group IV *significant at p<0.05.

Table (6) show there was significant difference in anti-CCP value between the studied groups with significantly higher level in Rheumatoid arthritis group in comparison to chronic hepatitis B&C group and significantly higher level in both chronic hepatitis B&C groups in comparison to control group.

**Table (6): Correlation between RF, as well as anti CCP titer, and both HBV DNA and HCV RNA**

| | RF | | Anti CCP | |
|---|---|---|---|---|
| | R | P | R | P |

| | | | | |
|---|---|---|---|---|
| HBV DNA | 0.902 | 0.001* | 0.569 | 0.001* |
| HCV RNA | 0.972 | 0.001* | 0.434 | 0.017* |

## Discussion:

As regard rheumatoid factor, interestingly the present study shows that there was significant difference between the studied groups with RF positivity of 0.00%(0) cases in control group, 4(13.3%) cases in chronic hepatitis B group, 6(20%) cases in chronic hepatitis C group and 24(80%) of cases in rheumatoid arthritis group.

Our study also shows that there was significant difference between the studied groups as regard anti CCP. In the comparison regarding anti- CCP positivity, there were no positive cases in control group. In HBV group, 3(10%) out of 30 patients had low positive anti CCP. Regarding HCV group, 4(13.3%) out of 30 patients had low positive anti CCP. Lastly, in RA group 6(20%) out of 30 patients had low positive anti CCP, 17(56.7%) out of 30 patients had high positive anti CCP and 7(23.3 %) were negative.

**Zengin et al., (2017)** whose study consisted of 44 patients with hepatitis B, 43 patients with hepatitis C, 25 patients with Rheumatoid arthritis and 46 healthy individuals as the control group. HBV and HCV groups and healthy control groups did not show a statistically significant difference between their RF and anti-CCP positivity. However, RA group had higher RF and anti-CCP levels and displayed a striking difference to the rest of the groups ($p < 0.001$ for each). The anti-CCP positivity levels were 20.5% (5 low positive, 3 moderate positive, 1 high positive), 32.5%, (9 low positive, 4 moderate positive,1 high positive) 72.4% (2 low positive, 2 moderate positive ,14 high positive) and 10.9% (all are of low positivity) for HBV, HCV and RA groups and healthy control group, respectively. As regard RF positivity they found 11.4% in HBV patients and 16.3% for HCV patients, 60 % in RA group and 2.2 % in control group. [16]

On the other hand **Sargin, (2018)**, enrolled 97 patients with chronic HBV infection, 35 patients with rheumatoid arthritis and 30 healthy as control group. The rates of positivity for RF and anti-CCP were 14.4% and 4.1% in patients with chronic HBV infection, respectively. RF positivity was detected in 14 of 97 patients with HBV infection and 10% in the healthy group. Of the 35 patients with RA, 23 were positive for RF, and 25 were positive for anti-CCP. Moreover, no anti-CCP positivity was detected in the healthy group. The rate of RF positivity was higher in RA patients than in patients with chronic HBV infection and healthy group. The rate of anti-CCP positivity was higher in patients with chronic HBV infection and RA patients compared to the healthy group. [17]

**Örge et al., (2009)** studied whether cyclic citrullinated peptide (CCP) antibody was useful for the diagnosis of RA in nonarthritic patients with HCV. Blood samples from 39 patients with chronic HCV infection, 87 normal sera from volunteer blood donors and 108 blood samples from patients with rheumatoid arthritis, from the rheumatology clinic, were taken. None of the patients with HCV infections had rheumatologic disease nor rheumatologic signs and symptoms, but 15% and 5% had antibody for RF and anti-CCP, respectively. When the results of the RA group were compared with other groups, the sensitivity, specificity and positive predictive value of the anti-CCP test was superior to the RF test.[18]

**Eltouky et al., (2019)** studied 150 non-arthritic chronic hepatitis C virus infection patients and found amongst 68 (45.3%) had positive RF& 82 (54.7%) had negative RF. HCV viral load did not vary in this research study between rheumatoid factor positive and negative research groups. A previous research study involved a large cohort of cases of around 271 study subjects having double-positive anti-HCV antibody and HCV RNA shows prevalence rates of positive rheumatoid factor and anti-CCP at 47.2% and 1.1%, consecutively.[19]

**Liu et al., (2008)** aimed to determine the prevalence of anti-CCP antibodies in HCV-infected patients with or without arthritis, rheumatoid factor (RF), or cryoglobulinemia. They studied

44 patients with RA, 34 patients with HCV infections, and 42 control patients concluding that patients with RA were more likely to have high titers of anti-CCP antibody than HCV-infected or control patients. A significant number of HCV-infected patients with neither RF nor cryoglobulinemia were also positive for anti-CCP antibodies (the three positive values were 36.10, 8.65, and 5.83 U/ml, P<0.01 compared with the control patients). [20] On the other hand **Lee et al., (2007)** examined 176 patients with chronic HBV infection who had no particular signs and found a high percentage of RF positivity 75 patient (42.7%) while detecting only one patient (0.4%) with anti-CCP positivity. [21]
Moreover, **Bombardieri et al., (2006)** found 23 within RA group (76.6%) were positive for anti-CCP antibodies and 27 (90%) for RF. Whereas within HCV group 15.4% were positive for RF but no patient was positive for anti-CCP antibodies. Notably, the prevalence of RF positive patients increased to 37.5% in patients affected by HCV presenting with articular involvement (3 of 8), and 66.7% in patients with RA-like polyarthritis (2 of 3). [22]
Interestingly **Hussein et al., (2016)**[23] showed that anti-CCP3 antibodies were specific100% for RA patients which indicate that anti-CCP3 antibodies are a very strong serum marker to differentiate RA from HCV patients. In this study they used anti-CCP3 antibodies, which may explain that difference in their results. **Sène et al.,** demonstrated the presence of anti-CCP antibodies in 5.7% of patients with HCV-related polyarthropathy and in 78% of patients with RA.[24] In addition, in the study of **Wener et al**. anti-CCP antibodies were present in 7% of patients with HCV-related polyarthropathy.[25] But both of them used anti-CCP2 antibodies.

**Conclusions**

Rheumatoid factor was found with considerable percentage in chronic HBV & HCV patients without musculoskeletal manifestations. Anti-CCP can be detected with low positivity in chronic HBV&HCV patients even without arthritic manifestations. There is a significant positive correlation between RF titre and HBV DNA& HCV RNA in chronic hepatitis patients. There is a significant positive correlation between anti-CCP and HBV DNA& HCV RNA in chronic hepatitis patients. Chronic HBV & HCV can be considered and investigated in patients with positive RF and/or anti CCP without arthritic manifestations.

## References:


1. Raihan R, Mohamed R, Hassan MRA, et al. (2017): Chronic Viral Hepatitis in Malaysia: Where are we now?. Euro asian Journal of Hepato-Gastroenterology; 7(1):65.
2. Puchades Renau L & Berenguer M (2018): Introduction to hepatitis C virus infection: Overview and history of hepatitis C virus therapies. Hemodialysis International; 22:S8-S21.
3. Lee MH, Yang HI, Lu SN, et al. (2011): Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: A community-based long-term prospective study. J Infect Dis; 206:469–477.
4. Corman S, Elbasha EH, Michalopoulos SN, et al. (2017): Cost-utility of elbasvir/ grazoprevir in patients with chronic hepatitis C genotype 1 infection. Value in Health; 20(8):1110-1120.
5. Alazawi W, Cunningham M, Dearden J, et al. (2010): Systematic review: Outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment. Pharmacol. Ther; 32:344–355.
6. Hong TP, Gow P, Fink M, et al. (2016): Novel population based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed. Hepatology; 63: 1205–1212.

7. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, et al. (2015): Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet; 386:1546-1555.
8. Vlachogiannakos J, Papatheodoridis GV (2018): Hepatitis B: Who and when to treat?. Liver International; 38:71-78.
9. Stanaway JD, Flaxman AD, Naghavi M, et al. (2016): The global burden of viral hepatitis from 1990 to 2013: findings from the global burden disease study 2013. Lancet; 388 :1081-1088.
10. Gottenberg, JE, Mignot S, Nicaise-Rolland, et al. (2005): Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjögren's syndrome. Annals of the Rheumatic Diseases; 64 (1):114-117.
11. Ingegnoli F, Galbiati V, Zeni S, et al. (2007): Use of antibodies recognizing cyclic citrullinated peptide in the differential diagnosis of joint involvement in systemic sclerosis. Clin Rheumatol; 26 (4):510–514.
12. Takasaki Y, Yamanaka K, Takasaki C, et al. (2004): Anticyclic-citrullinated peptide antibodies in patients with mixed connective tissue disease. Mod Rheumatol; 14 (5):367–375.
13. Lima İU, Santiago M (2010): Antibodies against cyclic citrullinated peptides in infectious diseases: A systematic review. Clin Rheumatol; 29:1345–1351.
14. Kappus MR, Sterling RK (2013): Extrahepatic manifestations of acute hepatitis B virus infection. Gastroenterol Hepatol (NY); 9 (2):123– 126.
15. Buzgan T, Karahocagil MK, Irmak H, et al. (2010): Clinical manifestations and complications in 1028 cases of brucellosis: A retrospective evaluation and review of the literature. Int J Infect Dis; 14 (6):469–478.
16. Zengin O, Yıldız H, Demir ZH, et al. (2017): Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies with hepatitis B and hepatitis C infection. Advances in clinical and experimental medicine: official organ Wroclaw Medical University; 26(6):987-990.
17. Sargin G, Kandemir A. (2018). Clinical utility of anti-cyclic citrullinated peptid and rheumatoid factor in chronic hepatitis B virus infection. Indian Journal of Rheumatology, 13(4):229.
18. Örge E, Çefle A, Yazici A, et al. (2010): The positivity of rheumatoid factor and anti-cyclic citrullinated peptide antibody in nonarthritic patients with chronic hepatitis C infection. Rheumatology International; 30(4):485-488.
19. Tamer WM, Eltoukhy MS (2019): Predictive Clinical Value of Rheumatoid factor and Anti-Citrullinated Protein Antibodies as Diagnostic Tools in Cases with Non-Arthritic Chronic Hepatitis C Viral Disease. United journal of Internal Medicine; 1(1): 1-4.
20. Liu FC, Chao YC, Hou TY, et al. (2008): Usefulness of anti-CCP antibodies in patients with hepatitis C virus infection with or without arthritis, rheumatoid factor, or cryoglobulinemia. Clinical Rheumatology; 27(4):463-467.
21. Lee SI, Yoo WH, Yun HJ, et al. (2007): Absence of antibody to cyclic citrullinated peptide in sera of non-arthritic patients with chronic hepatitis B virus infection. Clinical Rheumatology; 26(7): 1079-1082.
22. Bombardier C, Laine L, Burgos-Vargas R, et al. (2006): Response to expression of concern regarding VIGOR study. New England J Med.; 354(11):1196-9.
23. Hussein MS, Abdel Ghany SEA, Elashkar DS, et al. (2016): Anti-CCP hs (high sensitive) in Egyptian rheumatoid arthritis patients associated with chronic hepatitis C virus infection. The Egyptian Rheumatologist; 38(1):15-20

24. Sene D, Ghillani-Dalbin P, Limal N, et al. (2006): Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjögren's syndrome. Annals of the Rheumatic Diseases; 65(3):394-397.
25. Wener MH, Hutchinson K, Morishima C, et al. (2004): Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology; 50(7):2305-2308.