Study of the Complement Components and C-Reactive Proteins in Hepatitis Type C Patients

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Abstract. In order to study the complement components (C₃, C₄) and c-reactive protein (CRP), serum samples were obtained from patients infected with hepatitis type C, admitted to Marjan Hospital in Province of Babylon. The results indicated significant decrease in concentrations of both complement components of patients compared with apparently healthy persons. The components (C₃) concentrations were 134.875, 136.916 and 132.833 mg/dL for all patients, males and females patients respectively, while the components (C₄) concentration were 30.251, 34.501 and 26.001 mg/dL for all patients, males and females patients respectively. The results also showed that the percentages of positive c-reactive protein (CRP) were 33%, 50% and 17% for all patients, males and females patients respectively.

Key word: Hepatitis Type C, Complement component (C3), Complement component (C4), C-Reactive Protein (CRP).

1. Introduction.

Hepatitis type C virus (HCV) is the main causative agent of the liver chronic diseases, such as hepatocellular carcinoma and cirrhosis. They are also the most common causes of transplantation of the livers in many countries [1], especially in Australia, Europa, and the United States of America [2-3]. Approximately 170 million individuals are affected with these viral types worldwide [1]. Hepatitis type C viruses are enveloped viruses belonging to the genus hepacivirus from Flaviviridae family [4]. The genome of these viruses is single strand RNA with positive polarity and present within core of protein enclosed by bilayer lipid envelope containing two glycoproteins [5].

Interaction between hepatitis type C virus and the immune system of the host plays critical role in the pathogenesis and persistence of the this virus [6]. The complement system is a part of the innate and adaptive immunity, and this system consists from group of biochemical pathways which have the ability to remove the pathogenic components from the organism [7]. The components of this system produced by the liver, and they can link the innate and acquired immune response through different mechanisms, including activation of humoral immunity, modulating the function of T-cell, and regulating mechanisms of antibiotic effector [8]. The activation of the immune system leads to the excess of the cellular immune response that ranging from the opsonization to the apoptosis [9].

Several studies demonstrated that the complement system is involved in pathogenesis of different liver diseases, such as injury and repair, alcoholic, ischemic, fibrosis, and viral hepatitis [10]. This system
represent an important nonspecific defense mechanism of the host and involved protection against viral infections [11]. The hepatitis C virus infections causes weakness of the complement system through changing several components such as C₃, C₄ and C₉ [7, 12]. However, infections of hepatitis type C virus cause inhibition of C₃ and C₄ complement components expression [7, 13].

The monitoring of the C₄ complement component is appearing as specific tool to the follow of the hepatitis type C treatment [6]. Also the level of the C₄ complement component found to be associated with persistence and progression of hepatitis C disease [14]. The levels of the complement components C₃ are bring down in the serum of the hepatitis C patients [15]. The C₃ is a member of the acute phase proteins, and the expression levels of these proteins are either negatively or positively regulated by cytokines through inflammation processes [16-17].

The C-reactive proteins (CRP) are the major acute phase proteins produced by the liver. They may consider as mediator of tissue damage, and they have a capacity of activation the complement system [18-19]. The hepatitis type C virus causes producing cytokine-6 (IL-6) by the peripheral and circulating cells, which stimulate hepatic production of the C-reactive proteins, which are the main reactants of the acute phases [20].

2. Materials and Methods

2.1. Patients

This study involved twenty four (24) patients who were admitted to Teaching Marjan Hospital in Province of Babylon. People were diagnosed as infected with hepatitis virus type C according to HBs EIA Test Kit Package Insert (ACON Lab Inc. San Diego; USA) [21]. These patients were males and females. The study also involved twelve (12) healthy persons as a control group.

2.2. Samples

Blood samples were collected from patients and healthy individuals in sterile 10 mL tubes. Sera were prepared and used to study immune markers concentration, including complement components (C₃,C₄) and C-reactive protein (CRP).

2.3. Identification of the complement components

Complement components (C₃ and C₄) were identified in serum samples by radial immunodiffusion method using (Roseto degli Abruzzi (Te) Italy; LIOFILCHEM(R) s.r.i) as follow:

1. The RID EASY was removed from envelope, and plate was opened for around (5 minutes) at room temperature in order to get rid of any condensed water present in the wells.

2. The wells were filled with (5 μl) of non-diluted patients serum.

3. The dish was closed with a lid after placing the serum in the gel, and the envelope was closed and left at room temperature for 48 hours.

4. The diameters of precipitin rings were measured by using appropriate devices.

5. Complement components concentrations were determined by comparing rings formed with the company's on the attached schedules.
2.4. Identification of the C-Reactive protein-Latex (CRP-Latex).

Detection of the C-Reactive protein-Latex by the qualitative method (slide agglutination test) carried out using (LINER C KEMICALS S.L. Joaquim Costa 18 2a Planta. Barcelona, Spain) as follow:

1. The kit components and the patients serum were put at room temp.
2. drops of the patients serum were placed on the custom circuit in the tape test.
3. drop of C-reactive protein latex detector was added gently to the patients serum.
4. Well mixed then spread along the inner surface of the circuit in the strip of the test.
5. The slide was moved forward and backward for two minutes. The positive result in this method shown as agglutination.

2.5. Statistical analysis.

The results were analyzed by using the Statistical Package for Social Science (SPSS) [22] version 20 to calculate the Mean, Standard deviation, Standard error, Significant correlation at (0.01 and 0.05 level 2-tailed) and significant differences according to One Way A nova by descriptive excluded cases by cases with LSD at (95%) confidence and significant level of (P=0.05) present between complement components (C3) and (C4) within the study groups.

3. Results

The present results showed significant decrease in the concentrations of both complement components (C3) and (C4) in the hepatitis C patients when compared with healthy persons. In addition, the patients with hepatitis type C have showed positive results of the C-reactive proteins with different percentage among patients groups.

Table (1) shows that the mean of the complement component (C3) in mg/dL for all patients, males patients and females patients was 134.875, 136.916 and 132.833 respectively. All of these results were within normal reference value (90-180 mg/dL). Whereas the mean of the complement component (C3) in mg/dL for all persons, males and females were 177.751, 178.166 and 177.333 respectively and all these results were within the normal reference value (90-180 mg/dL).

Table (2) indicates that there is a significant difference of the complement component (C3) at P-value equal to 0.005 between all, males and females of patients and persons was 0.001, 0.002 and 0.003 respectively in mg/dL.

Table (3) mean of the complement component (C4) in mg/dL of all patients, males patients and females patients was 30.251, 34.501 and 26.001 respectively and which all these results were within normal reference value (20-50 mg/dL). Whereas the mean of the complement component (C4) in mg/dL of the all persons, males persons and females persons were 48.591, 48.733 and 48.451 respectively and which all these results were within the normal reference value (20-50 mg/dL).

Table (4) significant difference of the complement component (C4) at P-value equal to 0.005 was present between all, males and females of patients and persons was 0.001, 0.006 and 0.001 respectively in mg/dL.

Table (5) significant correlation is present between the (C3) of all patients with females patients (C3), all patients (C4) and females patients (C4). Also present between the males patients (C3) with all patients (C4) and females patients (C3). It is also present between the females patients (C3) with all
patients ($C_3$), all patients ($C_4$) and females patients ($C_4$). Moreover, the significant correlation is present between the ($C_4$) of all patients with all patients ($C_3$), males patients ($C_3$), females patients ($C_3$) and females patients ($C_4$). Also present between the females patients ($C_4$) with all patients ($C_3$), males patients ($C_3$), females patients ($C_3$) and all patients ($C_4$).

**Table 1.** Concentration of the complement component ($C_3$).

| Study groups   | Complement Component ($C_3$) in mg/dL | Statistical Analysis |
|---------------|--------------------------------------|----------------------|
| Patients      | Mean 134.875                         | Standard Deviation 40.169 | Standard Error 8.199 |
| Persons       | Mean 177.751                         | Standard Deviation 3.768  | Standard Error 1.087 |
| Males patients| Mean 136.916                         | Standard Deviation 41.803 | Standard Error 12.067 |
| Males persons | Mean 178.166                         | Standard Deviation 3.763  | Standard Error 1.536  |
| Females patients | Mean 132.833          | Standard Deviation 40.214 | Standard Error 11.609 |
| Females persons | Mean 177.333          | Standard Deviation 4.0824 | Standard Error 1.666  |

Normal concentration of complement component ($C_3$) according to the manufacture company Kit (90-180) mg/dL.

**Table 2.** Significant differences of Complement Component ($C_3$).

| Comparisons between the study groups (hepatitis C patients and apparently healthy persons) | Mean Difference | Standard Error | Sig. |
|------------------------------------------------------------------------------------------|----------------|---------------|------|
| Patients and Persons                                                                     | 63.001*        | 14.224        | 0.001|
| Male patients and Male persons                                                            | 63.833*        | 20.117        | 0.002|
| Female patients and Female persons                                                       | 62.166*        | 20.117        | 0.003|

*The mean difference is significant at the P-value= 0.05 level.

**Table 3.** Concentration of the complement component ($C_4$).

| Study groups   | Complement Component ($C_4$) in mg/dL | Statistical Analysis |
|---------------|--------------------------------------|----------------------|
| Patients      | Mean 30.251                          | Standard Deviation 12.359 | Standard Error 2.522 |
| Persons       | Mean 48.591                          | Standard Deviation 1.311  | Standard Error 0.378  |
| Males patients| Mean 34.501                          | Standard Deviation 12.576 | Standard Error 3.631  |
| Males persons | Mean 48.733                          | Standard Deviation 1.311  | Standard Error 0.535  |
| Females patients | Mean 26.001          | Standard Deviation 11.037 | Standard Error 3.186  |
| Females persons | Mean 48.451          | Standard Deviation 1.421  | Standard Error 0.581  |

Normal concentration of complement component ($C_4$) according to the manufacture company Kit (20-50) mg/dL.

**Table 4.** Significant differences of Complement Component ($C_4$).

| Comparisons between the study groups (hepatitis C patients and apparently healthy persons) | Mean Difference | Standard Error | Sig. |
|------------------------------------------------------------------------------------------|----------------|---------------|------|
| patients and persons                                                                     | 18.341*        | 3.543         | 0.001|
| male patients and male persons                                                            | 14.233*        | 5.011         | 0.006|
| female patients and female persons                                                       | 22.451*        | 5.011         | 0.001|

*The mean difference is significant at the P-value= 0.05 level.
Table 5. Significant correlation between Complement Components (C_3 and C_4).

| Complement Components (C_3,C_4) in mg/dL of hepatitis type C patients | Correlations | All (C_3) | Males (C_3) | Females (C_3) | All (C_4) | Males (C_4) | Females (C_4) |
|---|---|---|---|---|---|---|---|
| All | R=0.357 | R=1.001** | R=0.451* | R=-0.254 | R=0.606* |
| (C_3) | Sig.=0.255 | Sig.=0.001 | Sig.=0.027 | Sig.=0.426 | Sig.=0.037 |
| Males | R=0.357 | R=0.357 | R=0.705* | R=0.342 | R=-0.705* |
| (C_3) | Sig.=0.255 | Sig.=0.255 | Sig.=0.010 | Sig.=0.276 | Sig.=0.011 |
| Females | R=1.101** | R=0.357 | R=-0.606* | R=-0.254 | R=-0.606* |
| (C_3) | Sig.=0.001 | Sig.=0.255 | Sig.=0.037 | Sig.=0.426 | Sig.=0.037 |
| All | R=0.451* | R=0.705* | R=0.606* | R=0.010 | R=1.001** |
| (C_3) | Sig.=0.027 | Sig.=0.01 | Sig.=0.037 | Sig.=0.974 | Sig.=0.001 |
| Males | R=0.254 | R=0.254 | R=-0.254 | R=1.011 | R=1.011 |
| (C_3) | Sig.=0.426 | Sig.=0.276 | Sig.=0.426 | Sig.=0.974 | Sig.=0.974 |
| Females | R=0.606* | R=0.705* | R=0.606* | R=1.001** | R=1.011 |
| (C_3) | Sig.=0.037 | Sig.=0.011 | Sig.=0.037 | Sig.=0.001 | Sig.=0.974 |

**Correlation is significant at the 0.01 level (2-tailed).  
*Correlation is significant at the 0.05 level (2-tailed).

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Figure (1) transparent halos formed after 24 hours from placed the serum of hepatitis type C patients in the Complement Components (C_3) and (C_4) kit.

Figure (2) elevated in the concentration of persons complement component (C_3) in comparison with hepatitis type C patients of the all age categories.

Figure (3) increased in the concentration of male persons complement component (C_3) in comparison with male hepatitis type C patients of the all age categories.

Figure (4) raised in the concentration of female persons complement component (C_3) in comparison with female hepatitis type C patients of the all age categories.

Figure (5) elevated in the concentration of persons complement component (C_4) in comparison with hepatitis type C patients of the all age categories.

Figure (6) increased in the concentration of male persons complement component (C_4) in comparison with male hepatitis type C patients of the all age categories.

Figure (7) raised in the concentration of female persons complement component (C_4) in comparison with female hepatitis type C patients of the all age categories.
Figure 2. Comparison of complement component ($C_3$) between apparently healthy persons and hepatitis type C patients in mg/dL.

Figure 3. Comparison of complement component ($C_3$) between males apparently healthy persons and males hepatitis type C patients in mg/dL.

Figure 4. Comparison of complement component ($C_3$) between females apparently healthy persons and females hepatitis type C patients in mg/dL.
Figure 5. Comparison of complement component (C₄) between apparently health persons and hepatitis type C patients in mg/dL.

Figure 6. Comparison of complement component (C₄) between males apparently health persons and males hepatitis type C patients in mg/dL.

Figure 7. Comparison of complement component (C₄) between females apparently health persons and females hepatitis type C patients in mg/dL.
Table (6) the positive percent of C-reactive protein in hepatitis type C patients and apparently healthy persons was 33% and 0% respectively. Whereas the negative percent of this protein in hepatitis type C patients and apparently healthy persons was 67% and 100% respectively.

### Table 6. Percent of positive C-Reactive Protein (CRP) hepatitis type C patients.

| Study group               | Positive percent of CRP | Negative percent of CRP |
|---------------------------|-------------------------|-------------------------|
| Hepatitis type C patients | 33%                     | 67%                     |
| Apparently healthy persons| 0%                      | 100%                    |

Figure (8) percent of positive C-reactive protein of hepatitis type C patients and apparently healthy persons was 33% and 0% respectively.

Figure (9) percent of positive C-reactive protein of males hepatitis type C patients and males apparently healthy persons was 50% and 0% respectively.

Figure (10) percent of positive C-reactive protein of females hepatitis type C patients and females apparently healthy persons was 17% and 0% respectively.

![Figure 8](image1.png)

**Figure 8.** C-Reactive Protein percent comparison between patients and apparently healthy persons.

![Figure 9](image2.png)

**Figure 9.** C-Reactive Protein percent comparison between males patients and males apparently healthy persons.


4. Discussion

Tables (1 and 2) and figures (2 to 4) showed significant decrease in the concentrations of the complement component C3 of the patients compared with apparently healthy persons. These results agreed with [7], who found that this complements component significantly lowered in hepatitis type C patients. Tables (3 and 4) and figures (5 to 7) illustrated significant increase in the concentrations of the complement component C4 of the apparently healthy persons compared to patients. These results were agreed with [13], who found this complements component significantly decreased in hepatitis C patients. However, El-Fatah et al., demonstrated the C3 and C4 complement components were significantly reduced in the hepatitis C patients compared with healthy persons [23]. Talaat et al., found the concentrations of the components C3 and C4 complement were significantly lower in the patients of hepatitis C compared to healthy persons [24].

Recently, several studies have been reported that the proteases of the hepatitis C virus causes regulation in genes expression of complement components C3 and C4 as well as the genetic factors of the host like SNP Both of these leads to change in levels of these complement components in HCV disease [13, 25]. Decreasing in the concentration of the C3 and C4 of hepatitis C patients may reflect the consumption of complement or lower production due to the decrease in the functioning hepatocytes numbe. The livers are major synthesis sites of the complements components, so the reduce in levels of these components in the serum may reflect the defective or weakness of the liver cells which produces these complement components [26-27]. There are several reports have been supported the increasing consumption theory [28-29].

Table (5) showed the significant correlation between the complement components C3 and C4 between some of the study groups in case of the hepatitis C infection. Activation of the complement system provides defense barrier against of the viruses and viruses infected cells [30]. This system can be activated through classical, alternative and lectin pathways, and all of these pathways are converge at the components C3 which is a cleavage point and then forms the membranes attack complex (C5b-9) leading to cell lysis [31]. The classical pathway is induced by Clq binding to viral envelope and activation of the C1s and C1r with C1s esterase generation leads to C4 cleavage [31]. The binding of the components C3 and C4 also presents in apoptotic cells [32]. However, the complement components C3 and C4 produced by the liver [33]. And which are the major circulation proteins of the complement
The C-reactive proteins are opsonic part of pentraxins family, and these proteins can activate the complement system through binding to apoptotic cells [35].

Table (6) demonstrated that the positive percentages of the C-reactive protein in the hepatitis C patients was 33%, whereas the figures (8 to 10) showed that the positive percentage of this protein in the all patients, males patients, and females patients, were 33%, 50% and 17% respectively. Comparing the present results with other workers, Hussein., found the positive percent of C-reactive protein in hepatitis B patients of the all, males and females were 25%, 50% and 0% respectively [19]. While Kessel et al., found that the percent of this was 17% in hepatitis C patients [36]. Moreover, Afzal et al., established that the 45.8% of the hepatitis C patients had high positive percent of the C-reactive protein [37].

The cytokines have important role in inducing of immune responses against the hepatitis viruses. These cytokines include IL-1, IL-3 and TNF-α which are produced by the Kuppfer cells of the liver [18]. However, increase acute phase proteins production by the liver through increases secretion and production of these cytokines [38-39]. The cytokines such as IL-6 is produced in the no circulating and circulating cells, and this cytokines lead to synthesis of the acute phase protein especially C-reactive protein by the liver [40-41].

5. Conclusions.

The patients infected with hepatitis type C have low concentrations of the complement components C3 and C4. In addition, this infection type is associated with the presence of the C-reactive protein in the serum samples of all patients groups.

6. References

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