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The Vital Role of Cytotoxic T Cells in Iraqi COVID-19 Patients and Vaccinated Individuals

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Abstract

Coronaviruses, including the novel SARS-CoV-2, have led to a global pandemic, emphasizing the crucial role of T cells in mounting effective immune responses. This study investigates the correlation between cytotoxic T cells (CD8), vitamin D3 (VD3), and C-reactive protein (CRP) levels in a sample of Iraqi COVID-19 patients and vaccinated individuals. A total of 120 participants were included, comprising COVID-19 patients and vaccinated individuals. Samples were collected between October 2021 and February 2022. Reverse transcriptase polymerase chain reaction (RT-PCR) was used for COVID-19 diagnosis. VD3 and CD8 levels were determined using enzyme-linked immunosorbent assay (ELISA) kits, while CRP levels were measured via the ICHROMA system. Elevated VD3 levels were observed in COVID-19 patients (G1) and vaccinated individuals (G2), while CRP levels were notably higher in G1. CD8 levels were elevated in G1, G2, and individuals previously infected for 3-6 months (G3). While a significant correlation between CD8 and VD3 was noted, the association with CRP was not as pronounced. The findings underscore the importance of cytotoxic T cells in both natural and vaccinated immunity against COVID-19, highlighting potential avenues for further research and therapeutic interventions.

Keywords: COVID-19, cytotoxic T cells, vitamin D3, C-reactive protein

دور الخلايا التائية السامة في مرضى كوفيد-19 والأفراد الملقحين في العراق

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الخلاصه

أدى فيروس كورونا المستجد (SARS-CoV-2) إلى جائحة عالمية، مما أبرز الدور الحيوي للخلايا التائية في تحقيق استجابات مناعية فعالة. تبحث هذه الدراسة في العلاقة بين الخلايا التائية السامة(CD8) ، فيتامين د3(VD3) ، ومستويات البروتين المتفاعل C-(CRP) في مرضى كوفيد-19 والأفراد الملقحين في العراق. شملت الدراسة 120 مشاركًا، يتألفون من مرضى كوفيد-19 والأفراد الملقحين. تم جمع العينات بين أكتوبر 2021 وفبراير 2022. تم استخدام تفاعل البلمرة المتسلسل العكسي (RT-PCR) لتشخيص كوفيد-19. تم تحديد مستويات VD3 و CD8 باستخدام مجموعات الاختبار المناعي المرتبط بالإنزيم(ELISA) ، بينما تم قياس مستويات CRP عبر نظام ICHROMA , لوحظت مستويات مرتفعة من VD3 في مرضى كوفيد-19 (G1) والأفراد الملقحين(G2) ، في حين كانت مستويات CRP أعلى بشكل ملحوظ في G1

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.كانت مستويات CD8 مرتفعة في G1 و G2والأفراد الذين أصيبوا سابقًا لمدة 3−6 أشهر (G3) , في حين لوحظ ارتباط كبير بين CD8 وVD3 ، لم يكن الارتباط مع CRP بنفس القوة. تؤكد النتائج على أهمية الخلايا التائية السامة في المناعة الطبيعية والمكتسبة ضد كوفيد−19، مما يبرز إمكانيات البحث والتدخلات العلاجية المستقبلية.

1.Introduction

Coronaviruses, a viral class associated with gastrointestinal and respiratory disorders in both people and animals [1], usually target the upper respiratory tract, causing mild to severe illnesses such as the common cold or, in more serious cases, pneumonia. In December 2019, a surge of pneumonia cases with unclear causes emerged in Wuhan, China, attributed to the virus, which is currently known as SARS-CoV-2, infecting over 300,000 individuals worldwide by March 2020 [2].

The World Health Organization (WHO) declared COVID-19 a pandemic, witnessing widespread hospital admissions and deaths. Although the majority of COVID-19 cases are mild, a small number of severe instances have led to numerous organ dysfunctions, septic shock, and/or respiratory failure [3]. T cells play a crucial role in immune responses to COVID-19, with data suggesting their importance in combating serious viral infections [4]. T cell lymphopenia, exhaustion, and dysfunction correlate with illness severity in both SARS and COVID-19 [5]. The components of the adaptive immune system are B cells, CD8 + T cells, and CD4 + T cells. To neutralize infected cells, CD8 + T cells employ the primary histocompatibility class 1 pathway [6].

Early diagnosis of pneumonia can be achieved by measuring C-reactive protein levels, which have the potential to activate complement and boost phagocytosis. The CRP measurement, essential for identifying and evaluating severe lung infectious disease, was elevated in individuals suffering from severe pneumonia [7]. Numerous experimental investigations have demonstrated the modulation of both innate and adaptive immune responses by vitamin D3 (VD3), expressed in various immune cells, including naive or activated CD4+ and CD8+ T cells, B cells, neutrophils, monocytes, macrophages, and dendritic cells [8].

2. Materials and Methods

Between October 2021 and February 2022, a cross-sectional study that included one hundred and twenty patients of different ages (between 21 and 71) and sexes was conducted at various hospitals in Baghdad. The study protocol had been approved by the ethical committee of the University of Baghdad, Department of Biology (reference: CSEC/0122/0034).

The collection of each sample adhered to the following guidelines:

2.1 Patients

2.1.1. Group 1 (G1): Twenty patients who were hospitalized after 15–21 days of being diagnosed with COVID-19.

*2.1.2***.** *Group 2 (G2):* Twenty individuals were vaccinated with Pfizer and previously infected 21 days after receiving the second dose.

2.1.3. Group 3 (G3): Twenty previously infected patients 3-6 months after the date of their last infection (whether vaccinated or not).

2.1.4. Group 4 (G4): Twenty individuals were vaccinated with Pfizer 3-6 months after taking the second dose (G 4).

2.2. Control

2.2.1. Group 5 (G5): Twenty previously uninfected individuals who were vaccinated with Pfizer, received a second dose 21 days after the second dose (positive control).
2.2.2. Group 6 (G6): Twenty unvaccinated and uninfected individuals (negative control).

2.3. Laboratory Analysis

Nasopharyngeal swabs were collected from all patients diagnosed with SARS-CoV-2 infection using the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Kit (Zybio Inc., Germany). Blood from each patient was drawn and placed in a serum separator tube (SST) with a particular gel to sort the serum, which was then kept at room temperature for 15 minutes. After coagulation, sera were separated using a 4000xg centrifuge for 10 minutes to provide a clear serum for the CD8 test. The level of a human cluster of differentiation 8 (CD8) was detected by using the Enzyme-Linked Immunosorbent Assay (ELISA) kit (Cat. No. CSB-E12707h, CUSABIO, Houston, AUS) for the quantitative determination of CD8 concentrations in patients' serum. The level of human vitamin D3 (VD3) was detected by an ELISA kit (Cat No. MBS264661, My BioSource, CAL, USA) for the in vitro quantitative detection of human serum and organizations in the natural and recombinant VD3 concentrations. The C-reactive protein test (CRP) was detected using the ICHROMA System.

2.4. Statistical analysis:

The impact of various factors on the research parameters was found using statistical analysis. To compare means statistically, the Analysis of Variation (ANOVA) test with the least significant difference (LSD) was employed. The Chi-square test was used in this investigation to compare percentages (0.05 and 0.01 probability).

3. Results and Discussion:

3.1. Results comparing VD3 levels across different groups

The results illustrated in Table 1 reveal a high elevation in VD3 levels within G1 (41.9%), gradually decreasing in G2 and G3 (33.56%, 24.77%), respectively. A slight increase in VD3 levels was observed in G4 (25.98%). These rates apply to all patients. In the case of complete control (positive and negative), VD3 recorded the highest percentage at G6 (negative control) (31.22%), while it recorded a lower percentage at G5 (positive control) (25.69%).

Table 1: Comparison between different groups in D3

Group	Mean ± SE
	D3
G1: Patients	41.90 ±1.72 a
G2	33.56 ±2.04 b
G3	24.77 ±1.60 d
G4	25.98 ±1.44 cd
G5	25.69 ±1.68 d
G6: CO-	31.22 ±2.14 bc
LSD value	5.350 **
P-value	0.0001

Means having the different letters in the same column differed significantly. ** (P≤0.01).

3.2. Evaluation of CRP level in studied groups

In the patient groups, Table 2 shows a high level of CRP in G1 (38.51%), while a lower level was recorded in G2, G3, and G4 (2.79%, 2.53%, and 2.47%, respectively). Regarding the total control, CRP recorded lower rates in G5 (2.91%) and G6 (2.42%).

Table 2: Comparison between different groups in CRP

Group	Mean ± SE
	CRP
G1: Patients	38.51 ±2.12 a
G2	2.79 ±0.17 b
G3	2.53 ±0.12 b
G4	2.47 ±0.12 b
G5	2.91 ±0.18 b
G6: CO-	2.42 ±0.12 b
LSD value	4.305 **
P-value	0.0001
Means having the different letters in the same column differed significantly. ** (P≤0.01).	

3.3. Evaluation of CD8 levels in studied groups

Based on the current findings in Figure 1, high levels of CD8 were observed in G1, G2, and G3 (944.4%, 782.24%, and 850.25%), respectively. In contrast, there is a low level in G4 (293.88%) for the entire patient population, while CD8 displayed a lower proportion in G5 (309.2%) and G6 (259.48%) in the case of overall control (positive and negative) P-value 0.0001(P≤0.01).

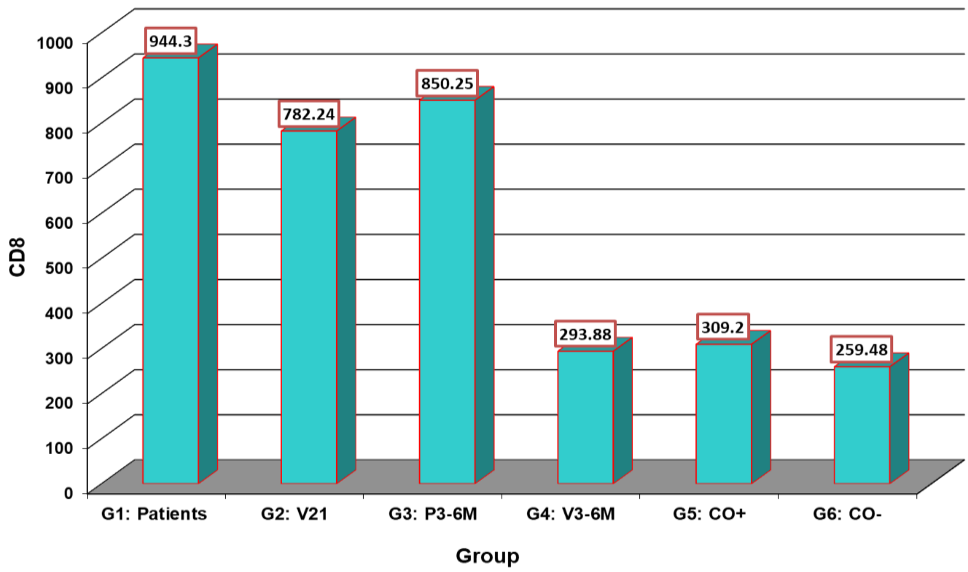

Figure 1: Comparison between different groups in CD8 level.

4. Discussion:

The acquired and innate immune systems become activated in response to viral infections. According to Diao *et al*.[9], the most efficient way to combat viral infections is by initiating the cellular immune response, specifically through T-cell activation. MacBride and Striker state that viruses can be eradicated from the host body by CD8+ cytotoxic T lymphocytes

(CTLs) that secrete various chemicals such as granzyme, perforin, and interferons (IFNs) [10,11].

The results illustrated in Figure 1 revealed high levels of VD3 in the different groups of patients with COVID-19, Pfizer vaccinated, and control groups (positive and negative). One of the reasons for the increase in VD3 levels in G1 (infected with COVID-19), G2 (vaccinated with Pfizer), and G3 (previously infected for 3-6 months, whether vaccinated or not) is the treatment protocol for COVID-19 patients, which includes medium-high doses of VD3; these percentages are expected to decrease at G4, G5, and G6; possibly due to not receiving any dose or receiving low dose of VD3.

These findings corroborate those of Murai *et al*. [12], who demonstrated the therapeutic benefit of vitamin D3 administration in COVID-19 patients. Two Brazilian hospitals admitted 240 COVID-19 patients, all randomly assigned to receive a single dosage of vitamin D3 (200,000 IU). At randomization, the mean 25 (OH)D levels in both groups were approximately 21 ng/mL, significantly higher than the mean 25 (OH)D levels in previous vitamin D3 studies. Vitamin D and its receptor, VDR, are essential for controlling the inflammatory process and remarkably affect both innate and adaptive immune responses. Vitamin D supplementation has been shown to have protective effects against viral acute respiratory infections in several observational studies and clinical trial meta-analyses [8].

The transfer of immune mechanisms requires vitamin D3. Vitamin D3's action may help raise awareness of the risks associated with COVID-19 [13]. Recent genomics-driven analyses of SARS-CoV-2 targets in human cells have identified vitamin D3 as one of the top three chemicals that exhibit promising patterns for mitigating infection through their influence on gene expression. Theoretically, vitamin D3 can reduce or prevent the catastrophic consequences of COVID-19 by controlling the renin-angiotensin-aldosterone system (RAAS), physiologic barriers, and innate and adaptive cellular immunity by binding to the vitamin D3 response elements (VDREs) in the promoter region of the target genes and activating or repressing those [14].

Viral replication and hyperinflammation are pathogenic factors in severe COVID-19, so vitamin D has attracted renewed attention considering the COVID-19 pandemic [15]. Analogous to vitamin D, ACE2 is the cell-surface entrance receptor for the coronavirus that causes SARS-CoV-2, or severe acute respiratory syndrome, and is directly impacted by vitamin D metabolites [16].

G1 patients had high CRP levels (38.51%), according to Figure 2, while lower values were seen in the other groups. Wang [17] demonstrated in his study that the moderate group had greater CRP levels and the most extensive lung lesion diameter than the mild group. These results are consistent with Wang's findings. Compared to the critical group, the CRP concentrations have been higher in the severe group than in the moderate group.
A statistically significant difference was observed. The breadth of the most extensive lung lesion and CRP titers elevated because the ailment progressed. These findings align with the results of Matsumoto *et al*. [18], who found a correlation between the increment in CRP levels and severe pneumonia, with both CRP levels and the width of the greatest lung lesion increasing as the disease progressed. According to Shang *et al*. [19], the severe group had higher C-reactive protein levels than the no-severe group. Furthermore, CRP was identified as an independent risk factor for severe COVID-19 disease.

The degree of the infection and lung lesions has been discovered to be correlated with CRP concentrations. This indicates that in the early stages of COVID-19, CRP levels may serve as a reliable indicator of both lung lesions and disease severity [17]. Age, sex, or bodily situations have no bearing on the CRP levels, which are directly correlated with the degree of inflammation [20]. Growing CRP in the first 48 hours of admission (a physiological score of respiratory function) is a better indicator of respiratory worsening than initial CRP levels or ROX (ratio of pulse oximetry) indices. There appears to be a biological relationship between CRP, the proinflammatory cytokine interleukin-6 (IL-6), and physiological indicators of hypoxemic respiratory failure. In COVID-19, elevated CRP indicates a possible respiratory deterioration and offers insight into the underlying mechanism.

The results depicted in Figure 3 show lower CD8 rates in other patient and control groups, with higher in G1, G2, and G3 groups. These findings coincide with the research by Ganji *et al*. [21], which indicated elevated CD8 levels. Another study by Urra *et al*. [22] revealed that ICU (Intensive Care Unit) patients had fewer CD8+ T cells in their blood than non-ICU patients. These data indicate that CD8+ T cells undergo a more dramatic change following SARS-CoV-2 infection than other lymphocyte subsets. Consequently, alterations in lymphocytes, especially CD8+ T cells, may indicate an impending disease worsening and clinical decline in COVID-19.

Subsets of lymphocytes and lymphocytes are essential for the immune system’s function. CD8+ T lymphocytes are essential to directly attack and eradicate virus-infected cells. In COVID-19 patients, there was a correlation between heightened T-cell fatigue, diminished functional diversity, and severe sickness [23,24]. Viral infection can also alter the numbers of some lymphocyte subsets [25]. Understanding the traits of the lymphocyte subsets in COVID-19 is, therefore, crucial since it may provide fresh perspectives on the functioning of the immune system.

During COVID-19, vitamin D deficiency may alter virus-specific immune responses, including T cell function, and promote adverse health outcomes in critically ill patients. The functional depletion of $CD8^{+}$ T cells is associated with severe SARS-CoV-2 infection [26,27]. A statistically significant difference in CD4+/CD8+ and CD8 cell counts was found between persons with low (Vitamone D) VitD plasma levels and those with greater VitD plasma levels, according to a study presented by Ricci *et al*. [28]. It was discovered that patients with low VitD plasma levels had a greater CD4/CD8 ratio. Numerous studies have shown that the vitamin D receptor (VDR), which is expressed in immune cells like B cells, neutrophils, monocytes, macrophages, activated or naive CD4+ and CD8+ T cells, neutrophils, and dendritic cells, influences both innate and adaptive immune responses [29].

Upon the initial onset of SARS-CoV-2 infection in humans, CD8+ T cells, CD4+ T cells, and antibodies specific to SARS-CoV-2 antigens are generated [30]. Each antibody and adaptive immune cell plays a distinct role in combatting the viral infection and ensuring the host's survival. When a virus infects a host, antigen-specific CD8+ T cells proliferate quickly to generate enough effector CD8+ T cells to kill the virus by cell-mediated cytolysis and release cytokines to protect the host against microorganisms that divide quickly [28]. A study published by Westmeier *et al*.,[31], SARS-CoV-2, shows that in mild COVID-19, there are no apparent CD4 T cell responses but robust CD8 T cell responses as indicated by the production of granzyme A, B, and perforin.

For SARS-CoV-2, an analogous immunological response might potentially be conceivable. Compared to CD4+ T cell responses, CD8+ T cell responses are more prominent in these viral infections. Therefore, close monitoring of CD8+ T cell responses is crucial to prevent the development of lung disease. The host's response to viral infections is dictated by the interplay between the organism's innate and adaptive immune systems [27]. Effective antiviral responses against viruses by the immune system depend on T cells, particularly CD8

T lymphocytes. Virally infected individuals showed alterations in their immunological states, especially variances in the usual CD8 ratio, due to the antiviral immune responses [32]. Growing evidence suggests that T cells are involved in COVID-19 and, most likely, the immunological memory that develops following recovery from SARS-CoV-2 infection. Data indicate that severe illness is associated with insufficient, excessive, or otherwise inappropriate T cell responses and that most, but not all; hospitalized patients appear to mount both CD8+ and CD4+ T cell responses [33,34].

Conclusion:

Effective antiviral responses against coronavirus disease require cell-mediated immunity, which includes T-cells (CD8). Increases in CD8 T cell values were linked to increases in inflammatory markers. VD3 and CD8 values were very high between COVID-19 patients infected for 15–21 days and individuals vaccinated with the first dose of Pfizer, which showed a significant increase. CRP with CD8 showed a high percentage in COVID-19 patients, while vaccinated individuals and other groups showed no significant differences between them.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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