

Complement System Response of Vaccinated Individuals with the Pfizer- Biontech and BBIBP-CorV (Sinopharm) Vaccines

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Received 2nd Jun 2023,

Accepted 3rd Jul 2023,

Online 5th Aug 2023

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Key words: SARS-CoV-2, COVID-19 vaccines, Complement system C3, Complement C4.

Abstract:

Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is an contagious illness that emerged in December 2019, remains a serious threat it has caused millions of deaths around the world, resulting in a global pandemic. COVID-19 vaccines protect against this severe illness through different approaches. Sinopharm and Pfizer-BioNTech COVID-19 vaccines were the greatest used vaccines in Iraq. Both vaccines have a specific mechanism to activate the immune system in human body.

This research aims to assessment the complement system C3 and C4 responses in vaccinated individuals with each the Pfizer-BioNTech COVID-19 vaccine or the Sinopharm vaccine.

Methods

The study included 180 Iraqi adults vaccinated with two doses, 1 week apart, using either the Sinopharm or Pfizer-BioNTech vaccine sixty person received the Pfizer vaccine, sixty person received the Sinopharm vaccine, and the other sixty subjects were un-vaccinated. After one week, the second dose was administered, and the blood samples were collected.

Results

study findings shown that Complement system 3 (C3) and (C4) levels were significantly increased (P -value= $<P<0.05$) in total vaccinated groups when compared with healthy control. also . the table was indicated C3 concentration was significantly high increased in first dose compared to second dose on vaccinated group , while the C4 concentration was non-significantly between two dose groups.

The study concluded that the Pfizer-BioNTech and Sinopharm vaccine boosted the immune system by high activation complement may also have a protective role and could function to enhance virus neutralization by antibodies, promote virus phagocytosis by immune cells, and lysis of coronavirus.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is caused COVID-19 was first recognized on Wuhan, China in December 2019 it is an infectious dangerous illness and spreads speedily, World Health Organization (WHO) has been classified as a global health problem [1]. Coronavirus virus causing severe pneumonia, multi-organ dysfunction, or may death in extreme cases of infection[2]. COVID-19 was spread by respiratory droplets when individuals sneeze, cough or exhale as well as may be spread by fomites [3]. There are many cases of asymptomatic carriers that made it difficult to control the epidemic in many countries around the world, Urgent need for a way to effectively stop the spread of the COVID-19 virus. Recently, many pharmaceutical companies have produced numerous vaccines [4,5].

The Pfizer/BioNTech is a lipid nanoparticle-based BNT162b2 COVID-19, It's the first United States Food and Drug Administration (FDA)-approved mRNA vaccine on December 2, 2020 is given in 2 doses three - weeks apart [6]. The demonstrated 95% efficacy of vaccine against symptomatic COVID-19 disease [7]. Pfizer-BioNTech Vaccine doesn't cause any serious side effects but often causes short-lived symptoms for example fatigue, mild fever, muscle aches and pain at the injection site [8].

The Sinopharm is attenuated or an inactivated COVID-19 vaccine, which is presently accepted by 65 countries [10], which are developed by destroying the virus' genetic material by chemicals, heating, or radiation while preserving all viral proteins intact. Thus, the whole virus vaccines are not infective but can still activate the immune system response [11].

The systemic and local signs of the covid-19 vaccine are different attributable to the immune response to the vaccination depends on various factors such as characteristics of the host age, sex, type of vaccine, composition, method of administration and many other factors[9].

1.1. Role of Complement in COVID-19

The complement system is a structured system consisting of more than 30 whey proteins; Many of them contain protease activity that enables one complement protein to activate another protein in a cascade [12], Which consider the "first line of defense" against entering viruses and as a bridge between innate and adaptive immune responses[13],

The adaptive immune response activated by classical pathway when happened interactions between complement protein C1q and antibodies bound to antigens immunoglobulin IgG or IgM, as well as, The classical pathway can also occur as an innate response activated by natural IgM or preformed auto-antibodies [14,15]. The remaining 2 pathways are innate immune responses that rapidly activate against pathogens in an antibody-in-dependent way cause include the mannose-binding lectin (MBL) pathway whereby directly binds to sugar particles attach to surface of pathogen, also, the alternative pathway that occurs by spontaneous activation of C3 on target cells [16]. The complement system supports immune body' ability to fighting COVID-19 infection and preserve homeostasis[17]. All three pathways leads to C3 protein activation and sub-sequent C5 activation cause cleavage of protein into the C3a and C5a subunits, which play a major role in pro-inflammatory responses and recruitment of immune cells(figure .1)[18].

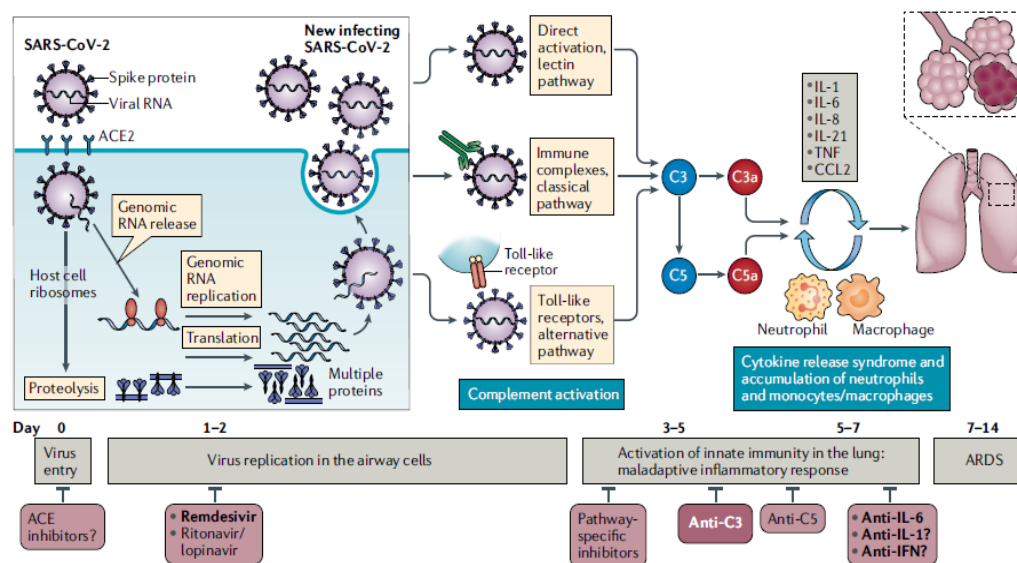


Figure -1- Complement activation with COVID-19 patients.

The C3b protein cleavage product can adhere to virus, tagging them for uptake and degradation (phagocytosis) by C3b receptors on immune cells [19]. Furthermore Pathogen clearance can be mediated by the C5b part, which forms part of the (MAC) membrane attack complex that attaches with membrane of target cell causing pore formation and lysis [19]. However, sub-lytic amounts of membrane attack complex on the surface of nucleated cells can instead play a role in pro-liferation and activation, as observed for Schwann cells and oligo-dendro-cytes [20]. Another important role of complement is improvement of antibody neutralization (n Ab) activity causing from C1q binding to Ab even in the non-existence of other complement proteins [21].

This study aims to determine the effectiveness of Complement system 3 (C3) and (C4) after first and second Pfizer-BioNTech and Sinopharm COVID-19 vaccines.

2. Materials and Methods

2.1. Study Design

In this research, a study was performed between December 2021 through September 2022. 180 male and female Iraqi nationals from a Al-Diwaniyah city in Iraq .were conducted in this study. Their age ranged from 20 to 60 years old divided to 60 individuals received the Pfizer vaccine , 60 received the Sinopharm vaccine and 60 unvaccinated individuals formed the control group . Information about the Iraqi people was collected using a standardized questionnaire platform. The form was divided into three main sections, which were listed in the following order: demographic information, such as age, gender, and place of residence; clinical information, such as prior COVID-19 infection ; chronic disorders, drug utilization history, and vaccine details, such as the type of vaccine, number of dose (first or second) severity and duration of any side effects.

The study was approved by the Senior Ethics Committee Public Health Department in the province. Written consent was taken from each vaccine recipient after explaining the purpose of the study.

2.2. Sampling Collection

The specimens were taken one week after the first and second vaccination injection. 5mL of whole blood was drawn from each individual and placed in gel tubes and centrifuged for 15 min at 4000 rpm. The serum was then split into three parts, placed in Eppendorf tubes, and stored at 20°C until use.

2.3. Inclusion and Exclusion Criteria

The adults Iraqi from Al Diwaniyah Governorate, who received two doses of the COVID-19 vaccine (Pfizer-BioNTech and Sinopharm) and who agreed to participate were included in this study with involved the Individual have pre-existing COVID-19 infection, who received only the first or second dose of the above-mentioned COVID-19 vaccines, and those who did not receive the second dose during the proposed period .

2.4. Immunological Biomarkers Measurement

The direct ELISA technology was Used to Measurement human Complement system 3 (C3) and (C4) . It is suitable for in vitro semi-quantitative detection of human serum, A 5 μ L was added to the ELISA plate then added 495 μ L of the dilute solution(DS), followed by 2 stages of washing then drying. The reaction was stopped by adding a stop solution. Lastly, use the ELISA reader at a wavelength of 450 nm to read plate ,The results were then calibrated with the standard curve and final values were extracted.

2.5. Statistical Analysis

The data were subjected to ANOVA analysis at a probability level of 0.05, and then using Graph Prism 7 program for knowing the significant differences of the studied criteria included.

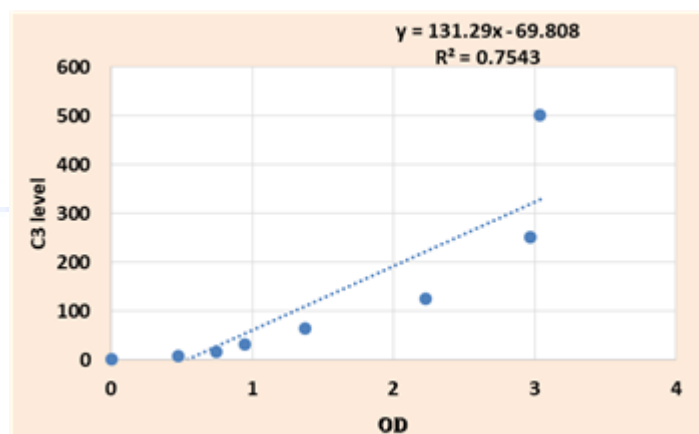


Figure.3.3. Standard curve for human C3 by ELISA

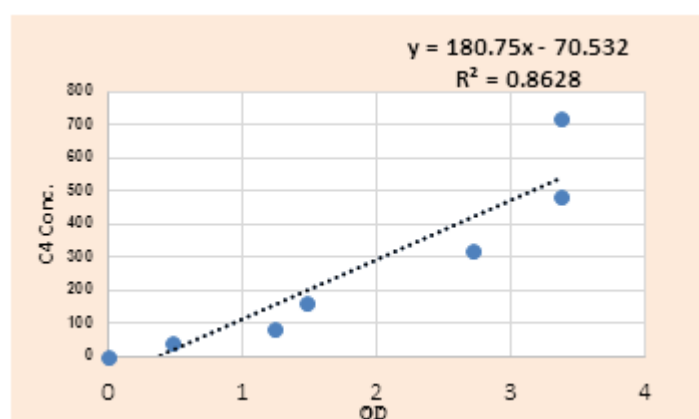


Figure.3.2. Standard curve for human C4 by ELISA

3. Results

The present study showed that serum Complement system 3 C3 and C4 levels were significantly increased (P-value= \leq P<0. 05) in total vaccinated groups when compared with healthy control as

shown in table (3.1) . Also, the table was indicated C3 concentration was significantly high increased in first dose compared to second dose vaccinated group , while the C4 concentration was non-significantly between two dose groups as shown in table (3.2).

Table (3.1) Descriptive analysis of serum Complement C3 and C4 .

Parameters	Control	patients	Calculated P value
	Mean ±Standard error range		
C3	3.19±0.29 (1.078-7.302)	13.51±1.74 (2.53-52.12)	0(S)
C4	23.07±2.48 (3.5-60.64)	53.99±2.17 (7.33-118)	0(S)
S: Significant difference at P<0.05			

S: Significant difference at P<0.05

Table (3.2) Descriptive analysis of serum Complement C3 and C4 levels two dose of vaccines

Parameter		Control	Dose (1)	Dose (2)	P value
C3	Mean\pm SE	3.19 \pm 0.29	21.38 \pm 2.8	5.64 \pm 0.41	0(S)
	Range	1.078-7.302	4.03-52.12	2.53-13.78	
C4	Mean\pm SE	23.07 \pm 2.48	56.18 \pm 1.9 4	51.79 \pm 3.89	0(S)
	Range	3.5-60.64	28.77- 92.64	7.33-118	

S: Significant difference at P<0.05

4. Discussion

The complement system is soluble glycoproteins, a part of the innate immune system was discovered by Jules Bordet (1895) as a heat-labile component mainly produced by produced by hepato-cytes and circulating in the extracellular fluid and blood [22] which play as anti-inflammatory roles for rapidly recognizing and clearing pathogens, apoptotic cells and cellular debris also a dominant participant in antibody-mediated pathogen killing , clearance and contributes to directing activation the adaptive response[23]

The result of present study is nearly similar to Mellors *et al.*,(2020) [24] they proved vaccination by the inactivated virus (Sinopharm) vaccine ability to induce the complement component C3 and C4 in human vaccinated compared with non-vaccinated ,specially C3 activation were observed high level in the lung as early as 1 day after covid-19 infection or first vaccination .Furthermore, Aschenbrenner *et al.*,(2021) [25] who they proved that the complement protein C3 and C4 are significantly increased in total vaccinated groups when compared with healthy control after covid-19 Vaccine dose , particularly high concentrations of C3 in plasma the highest level of all complement factors in first dose compare to C4 concentration [26] . Also , study of Pisanic *et al.*,(2020) has demonstrated that all vaccinated and recovering people had significantly increased spike-specific Abs of diverse Ig isotypes with complement component C3 and C4 in human after mRNA (Pfizer) COVID-19 vaccine [27].

On the other hand the result of present study is in agreement with Zinellu *et al.*, (2021) [28] who indicated that C3, C4 complement levels were significantly lower in COVID-19 patients compare with control group similar to Dheir *et al.*, (2020)in his study showed there is no significant difference to complement levels of C3 and C4 protein in COVID-19 patients[29]. .

Alternative pathway that occurs by spontaneous activation of C3 activation during the first week of COVID-19 infection where C3 attaches to the surface of viruses and may be carried intra-cellularly ; however, the ability of viruses to cleave C3 may affect host antiviral responses [30]. This may explain the findings of our results of the study, as it confirmed that the increase in the concentration of C3 because it is one of the direct activity of Alternative pathway of after entering the COVID-19 vaccine, which leads to an increase in the level in the first dose , and the increase in activity may lead to the consumption and lower levels of C3 in the second dose, which facilitates the activity of other complement methods that depend on the concentration of C4 levels (involved in classical and MBL pathways) as the response of complement system activity after infection and vaccine varies from one person to another. all three pathways leads to C3 protein activation and subsequent C5 activation, This involves protein cleavage into the activated C3a and C5a subunits, which play a major role in pro-inflammatory responses and recruitment of immune cells. The C3b cleavage product can adhere to pathogens, tagging them for uptake and degradation (phagocytosis) by C3b receptors on immune cells[31,32].

The complement system is part of the innate immune system that enhances the clearance of antibodies (Ab) , phagocytes, stimulates inflammation, and attacks the cell membranes of pathogens[33] . Also, can neutralize non-enveloped or enveloped viruses in situation of virus infection , Following Covid-19 infection, macrophages are induced by the complement system to produce pro-inflammatory cytokines like IL6 and IL-1b [34].

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