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The Effect of *Coronavirus* –Disease 2019 on Total Immunoglobulins among Hospitalized Patients at Khartoum State, Sudan 2022

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Abstract **Background:** the novel coronavirus disease 2019 (Covid19) pandemic, caused by Sars-Cov-2, poses an unprecedented dare to clinicians and strain on the healthcare system due to its high rate of infectivity (R_o) and mortality. The purpose of this study is to detect the effect of Sars-Cov-2 on total immunoglobulin among hospitalized patients at Khartoum state. **Methodology:** this study is observational, case-control study design, conducted in quarantine center at Jabra hospital for emergency and injuries. PCR confirmed covid19 patients were identified, and non-covid19 individuals were recruited. About 3-4 ml of blood sample was withdrawn from each participant, the blood samples that obtained were centrifuged, and plasma that obtained was processed by using fully closed system, auto-chemistry analyzer CS-T180 (DIRUI), the principle of the test based on the turbidimetry. **Results:** A total of 52 participants were enrolled in this study. Total plasma IgA, IgG, and IgM were measured for each participant, P. value ≤ 0.05 considered to be statistically significant. The study revealed that the total plasma IgA was higher than normal range in 7 patients (21.9%), and was lower in 1 patient (3.1%). The mean of total IgA was higher in study group compared to control group (P. value < 0.05). The study also showed that the total IgG was higher in 1 patient (3.1%). Also the mean of total IgG was higher in study group compared to control group (P. value < 0.05). The study found that the total IgM was lower in 3 patients (9.4%). Interestingly the mean of total plasma IgM was higher in control group compared to study group (P. value < 0.05). **Conclusion:** we conclude that the SARS-Cov-2 infections leads to increase in the total amount of IgA and IgG while decreases the total amount of IgM. Therefore, covid19 has direct effect on total immunoglobulin.

Keywords: *Covid19, humoral immunity, immunoglobulins, IVIG, Sars-Cov2, Sudan*

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1. Introduction

A newly described *coronavirus* emerged in 2002, which named severe acute respiratory syndrome (*SARS)* – associated *coronavirus* (*Sars– Cov*) the virus causes an atypical pneumonia called *SARS*, a dangerous and probably life – threatening viral infection of humans [1,2,3]. The genera coronaviruses belong to *Coronaviridae* family. They were so named because of the crown – like shape of their virions under electron microscope. These viruses considered the second most important causative agent of common cold, *rhinoviruses* being the first causative agent. [1,2,3] in late December 2019, a group of patients were admitted to hospitals with an initial diagnosis of pneumonia of unknown etiology. These patients were epidemiologically linked to a seafood and moist animal wholesale market in Wuhan, Hubei province, china [4].

The novel *coronavirus* disease 2019 (covid19) pandemic, caused by severe acute respiratory syndrome coronavirus -2 (*Sars-Cov-2*), poses an unprecedented dare to clinicians and strain on the healthcare system due to its high rate of infectivity (R_o) and mortality [5]. Particularly in countries where the healthcare sector was already deteriorated. Covid19 symptoms can range from mild to severe disease, and manifest 2 – 14 days after you are

exposed to the virus that causes covid19.Which can include cough, fever, shortness of breath or difficulty breathing, fever or chills, muscle or body aches, vomiting or diarrhea, and new loss of taste or smell [6]. Severe covid19 is characterized by pneumonia, dyspnea, hypoxemia, hyper inflammation, and lymphocytopenia, it can rapidly progress to respiratory failure and acute respiratory distress syndrome (ARDS) which is associated with higher risk of mortality [7].

World health organization (WHO) declared the *Sars –CoV-2* outbreak as a public health emergency of international concern (PHEIC) [8]. During the week 20-26 December 2021, following a progressive increase since October, the world number of new cases were increased by 11% as compared to the previous week, while the number of new deaths remained similar to the number reported during the previous week. This corresponds to just under 5 million new cases and over 44.000 new deaths [9]. As of 26 December, over 278 million cases and just under 5.4 million deaths have been reported globally [9]. The areas of the Americas reported the largest increase in new cases in the last week (39%), followed by the African region which announced an increase of 7%. The African zone reported the highest increase in the number of new deaths (72%), followed by the south-east Asia region (9%) and the region of the Americas (7%) [9].

Pneumonia is the major cause of morbidity and mortality in covid19, unluckily, the lack of an effective antiviral agent and vaccine further complicates the situation and calls for further intensification in research [10]. Preventive measures are the most important strategy to limit the expansion of cases. Early screening, diagnosis, isolation, and supportive treatments of symptomatic patients are necessary to prevent future spread. Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. The most important strategy for the populations to undertake is to considerably wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment. To minimize the risk of transmission in the community, individuals should be advised to wash hands diligently, practice respiratory hygiene (such as covering their coughing or sneezing) and avoid crowds, and close contact with ill individuals; if possible Social distancing is advised, particularly in places that have community transmission [11].

1.1. Immunoglobulin as Immune Modulator

In parallel with the development of new agents, it is wise to search the efficacy of existing therapeutic options with an acceptable safety profile, the administration of intravenous immunoglobulin (IVIG) represent such an example [10]. In the context of covid19, the actual role of IVIG is not to boost the immune system, but via its immunomodulatory effect to suppress a hyperactive immune response that is seen in some patients, this massive response which is ambiguously described as cytokine storm syndrome, ends up being the main cause of lung injury, this highlight the importance of selecting the right patients and intervening at the right moment [10]. Former data indicate that exaggerated immune response by the host is of greater importance for covid19 progression than virus induced damage alone. Therefore, down modulation of hyper-inflammation in severe covid19 patients is of major importance [12]. Available immunomodulatory drugs are intravenous immunoglobulin preparations [12]. It might be believed that IVIG could be used in covid19 patients and be one of worthwhile therapeutic options [13].

1.2. Immunoglobulins Mechanism of Action

A variety of mechanisms of action have been attribute to the beneficial effects of IVIG, including their interaction with T-cell function, antigen presenting cell maturation /presentation, combined with their capacity of “tuning down” inflammatory reactions. Thus, these therapeutic properties of IVIG seem to be suitable in particular for Covid19 severe infection, where an inaccurate adaptive immune activation and inflammation with consequence coagulation abnormalities, are all involved in the pathogenesis of the disease [14]. Immunoglobulins (Igs) are highly diverse autologous molecules able to improve the immunity in different physiological and sickly conditions they have a role in the development and function of both B and T lymphocytes [15].

Currently, there is no consensus on treatment algorithms for covid19, as the evidence available is not well controlled and largely based on personal accounts rather than facts or research [5]. Given rapid and catastrophic spread of covid19, there is an urgent need to explore preexisting therapeutic options while novel therapies and vaccines are being developed. Intravenous immunoglobulin (IVIG) is a product derived from the plasma of thousands of donors used for treatment of primary and secondary immunodeficiency, autoimmune / inflammatory conditions, neuroimmunologic disorders, and infection–related complication [5]. Available immunomodulatory drugs are have been used for treatment of inflammatory diseases for decades, and first clinical studies have showed promising results in treatment of covid19 patients [16].

2. Material & Methods

2.1. Study Design, Area, and Populations

This is observational, case – control study design, which conducted in quarantine center at Jabra hospital for emergency and injuries at Khartoum state, Sudan. The study conducted on Covid19 patients aged (45-70) years who lived in Khartoum state. A total of fifty two (n=52), 32 cases and 20 healthy controls were participated in the study. Convenience non probability sampling technique was applied in this study, from 03/02/2022 up to 01/03/2022.

2.2. Data Collection, Processing and Analysis

PCR confirmed covid19 patients were identified in Jabra hospital, and non-covid19 individuals were recruited,

Personal data (name, gender) was obtained from the participants, then about 3-4 ml of blood sample was withdrawn from each participant. The blood samples that obtained from the patients and healthy individuals were centrifuged, and plasma that obtained, was processed by using fully closed system, Auto-Chemistry Analyzer CS-T180 (DIRUI), the principle of the test based on the turbidimetry. The data that was collected from the participant and laboratory results were analyzed by using statistical package social science (SPSS) computerized program version 16.

2.3. Ethical Approval Statement

Approval to conduct this study was obtained from the research ethics committee of Alzaiem Alazhari University (faculty of medical laboratory sciences). Permission from the Jabra hospital was applied, and verbal consent was obtained from the participant before proceeding with the study.

3. Results

A total of 52 participants were enrolled in the recent study aged (45-70 years), 32 (61.5%) were covid19 patients, and 20 (38.5%) healthy participants as control group. Among covid19 patients 18/32 (56.2%) were male and 14/32 (43.8%) were female, and among healthy control group 8/20 (40%) were male and 12/20 (60%) were female, as shown in Table 1.

Total plasma IgA, IgG, and IgM were measured for each participant, chi-square test was performed for (proportion) and T-test performed for (mean), P. value ≤ 0.05 considered to be statistically significant

The recent study showed that the total plasma IgA was within the normal range among all control group (healthy participants) 20(100%). on the other hand, among study group (covid19 patients) the total IgA was lower than normal range in 1 patient 3.1% within the study group, IgA was within the normal range in 24 patients 75% within the study group, and it was higher than normal range in 7 patients 21.9% within the study group, as shown in Table 2.

The mean of total IgA was higher in study group (covid19 patients) compared to control group (healthy participants) (p. value < 0.05) as shown in Table 3.

The recent study also revealed that the total plasma IgG level was within the normal range among all control group (healthy participants) 20(100%), among study group (covid19 patients) the total plasma IgG was within the normal range in 31 patients 96.9% within the study group, IgG was higher in 1 patient 3.1% within the study group, no low level of plasma IgG was detected as shown in Table 4.

Also the mean of total IgG was higher in the study group (covid19 patients) compared to control group (healthy participants) (p. value <0.05) as shown in Table 5.

Table 1. gender frequency among the control group and the study group

Category		Frequency	Percent
Control group (healthy participants)	Male	8	40.0%
	Female	12	60.0%
	Total	20	100.0%
Study group (COVID19 patients)	Male	18	56.2%
	Female	14	43.8%
	Total	32	100.0%

Table 2. Distribution of plasma IgA levels within the control group and study group

Category		IgA levels			Total
		Lower than normal range	Within normal range	Higher than normal range	
Control group (healthy participants)	Count	0	20	0	20
	% within control group	0%	100.0%	0%	100.0%
Study group (COVID19 patients)	Count	1	24	7	32
	% within study group	3.1%	75.0%	21.9%	100.0%

Table 3. Comparison of plasma IgA mean between control group and study group

	Category	Mean	S.D	P. value
IgA mg\dl	Control group (healthy participants)	221.4	66.6	0.006
	Study group (COVID19 patients)	308.2	123.0	

Table 4. Distribution of plasma IgG levels within the control group and study group

Category		IgG levels			Total
		Lower than normal range	Within normal range	Higher than normal range	
Control group (healthy participants)	Count	0	20	0	20
	% within control group	0%	100.0%	0%	100.0%
Study group (COVID19 patients)	Count	0	31	1	32
	% within study group	0%	96.9%	3.1%	100.0%

Table 5. Comparison of plasma IgG mean between control group and study group

	Category	Mean	S.D	P. value
IgG mg\dl	Control group (healthy participants)	840.8	175.1	0.0001
	Study group (COVID19 patients)	1084.3	208.4	

The recent study also showed that the total plasma IgM was within the normal range among all control group (healthy participants) 20(100%), whereas among study group (covid19 patients), the total IgM was lower than normal range in 3 patients 9.4% within the study group, IgM was within normal range in 29 patients 90.6% in the study group, no high level of plasma IgM was detected as shown in Table 6.

Table 6. Distribution of plasma IgM levels within the control group and study group

Category		IgM levels			Total
		Lower than normal range	Within normal range	Higher than normal range	
Control group (healthy participants)	Count	0	20	0	20
	% within control group	0%	100.0%	0%	100.0%
Study group (COVID19 patients)	Count	3	29	0	32
	% within study group	9.4%	90.6%	0%	100.0%

Interestingly the mean of total plasma IgM was higher in control group (healthy participants) compared to study group (covid19 patients) (P. value < 0.05) as shown in Table 7.

Table 7. Comparison of plasma IgM mean between control group and study group

	Category	Mean	S.D	P. value
IgM mg\dl	Control group (healthy participants)	135.1	32.6	0.004
	Study group (COVID19 patients)	96.8	50.3	

Table 8. Comparison of plasma IgA, IgG and IgM mean within gender in COVID19 patients

Category	Gender	N	Mean	SD	P .value
IgA mg\dl	Male	18	321.4	126.6	0.4
	Female	14	287.3	119.5	
IgG mg\dl	Male	18	1082	211.7	0.9
	Female	14	1087	211.8	
IgM mg\dl	Male	18	86.3	47.7218	0.1
	Female	14	110.2	51.9728	

The recent study revealed that there was no difference in the mean value of IgA, IgG, and IgM between gender within covid19 patients P. value was 0.4, 0.9, and 0.1 respectively as shown in Table 8.

4. Discussion

The rapid international spread of SARS – Cov-2 virus induced Covid19 disease leads to an urgent demand for appropriate therapeutics. The major issue for severe covid19 patients is a dysregulated immune system with hyper inflammation, cytokine storm, ARDS, and eventually respiratory failure [16]. Previous data indicate that in severe cases excessive immune response, mediated by neutrophils, is of greater importance for Covid19 progression than virus induced damage alone, highlighting the importance of immune modulators [16].

We present our assumption that administration of IVIG within a specific dosage would be extremely beneficial towards reducing mortality and probably even the length of hospitalization of patients exhibiting severe Covid19 symptoms. Administration of IVIG in severe and critical Covid19 patients was safe, increased the likelihood of survival and reduced the risk of disease progression [17].

The aim of this study was to detect the effect of Covid19 on total immunoglobulin namely IgA, IgG, and IgM. In this observational case-control study which performed on 52 participants 32 (61.5%) Covid19 patients and 20(38.5%) healthy control during one month period, we found that among all control group (healthy participants) the total amount of IgA was showed to be within normal range, whereas among study group (Covid19 patients) 7 cases (21.9%) were showed high amount of total IgA, this might be due to the SARS – Cov-2 preferred portal of entry which is the mucosal surfaces of upper respiratory tract and conjunctiva [18]. that induce the production of secretory IgA. Our finding also demonstrated that the total IgG level was normal among all control group (healthy participants), whereas among study group (Covid19 patients) the total IgG was higher in 1 case (3.1%) and within normal range among others.

Our study also demonstrated that the total IgM level was within normal range among all control group (healthy participants), while among study group (Covid19 patients) the total IgM was lower in 3 cases (9.4%), this slight reduction might indicate antibody class switching to IgA and IgG as a result of SARS –Cov-2 infection.

The recent study revealed that there is increase in the mean value of IgA, and IgG among study group compared

to control group, such significant increases can be attributed to the hypothesis of hyper immune response that seen in Covid19 patients. Whereas the mean of total IgM was higher in control group compared to the study group this might be due to the antibody class switching in Covid19 patients to IgA and IgG classes as mentioned earlier. Unfortunately, up to date there is no international published studies similar to the current one.

Our study demonstrated that there is no difference in the mean value of IgA, IgG and IgM between genders within Covid19 patients.

5. Conclusion

1. We conclude that the SARS – Cov-2 infections can lead to increase in the total amount of IgA and IgG while decreases the total amount of IgM. Therefore, covid19 has direct effect on total immunoglobulin. Thus we support the idea of using IVIG as immune modulation to modulate the immune response.
2. We recommend conducting study to measure the level of inflammatory and anti-inflammatory cytokines among severe covid19 patients at Khartoum, to prove the hypothesis of cytokine storm as a result of hyper immune response as showed in our study, and to associate it with our finding.
3. We also recommend conducting controlled clinical trials on covid19 patients in Sudan, by using IVIG in appropriate dosage, to obtain a clear picture of using IVIG as immune regulator and as a therapeutic option in Covid19 patients.

Conflicts of Interest

We confirm that there are no known conflicts of interest associated with this research and there has been no significant financial support for this work that could have influenced its outcome.

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