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Evaluation of Serum Anticardiolipin Antibodies and D-dimer in Recipients of COVID-19 Vaccines in Ado-Ekiti, Ekiti State, Nigeria

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ABSTRACT: Coronavirus disease 2019 (COVID-19) manifests itself in a variety of ways, implying a wide range of host autoimmune responses which could lead to disseminated intravascular coagulation. This study was designed to evaluate serum anticardiolipin antibodies and D-dimer in recipients of COVID 19 vaccines in Ado-Ekiti, Ekiti State, Nigeria. The study population comprised sixteen (16) fully vaccinated subjects, fifteen (15) partially vaccinated subjects and fifteen (15) unvaccinated subjects (control). Anticardiolipin antibodies and D-dimer were analyzed using ELISA. D-dimer and anticardiolipin antibodies were significantly higher in fully and partially vaccinated subjects compared to control ($p<0.05$). D-dimer and anticardiolipin were insignificantly higher in fully vaccinated subjects compared to partially vaccinated subjects ($p>0.05$). Anticardiolipin and D-dimer were significantly higher in recipients of mRNA vaccines compared to viral vector vaccines ($p<0.05$). This study discovered that recipients of the COVID-19 immunization have a higher risk of developing antiphospholipid syndrome due to increased anticardiolipin. If disseminated intravascular coagulations is present and its complications are not adequately handled, this could become more serious.

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Coronavirus disease 2019 (COVID-19) is a respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Lai *et al.*, 2020). The virus is a member of the coronavirus family, which are zoonotic pathogens, meaning that they cause and spread illnesses between humans and a variety of animal species, including cattle, camels, cats, and bats (El-Sayed *et al.*, 2021). The first cases of COVID-19-related infection were reported in December 2019 in Wuhan, Hubei Province of China, and were linked to the Huanan Seafood Market. The infection has since spread to over 216 countries and territories (Dhama *et al.*, 2020). The World Health Organization (WHO) declared COVID-19 a pandemic on January 30, 2020 and declared it a global pandemic in March 2020. Upper respiratory tract infections (URTIs), such as the common cold, are typically caused by common human coronaviruses. Some variations, however, can result in mild flu-like symptoms. At first, SARS-CoV-2 cases were linked to significant fatality rates, particularly in persons with chronic illnesses including diabetes and

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cardiovascular disorders (Cucinotta & Vanelli, 2020). COVID-19 can also trigger a cytokine storm in pulmonary tissues through hyperactivation of the immune system and the uncontrolled release of cytokines. The phrase " cytokine storm" is a descriptive term to encompass a variety of events that may ultimately result in multi-organ failure and death (Montazersaheb *et al.,* 2022). However, there is no known precise molecular mechanism defining cytokine storm, and developing a mechanistic knowledge of how SARS-CoV-2 induces a hyperactive inflammatory response is important for developing effective treatments (Hirawat *et al.,* 2021).D-dimer is a fibrin degradation product that is generated during the breakdown of blood clots in the body by an enzyme called plasmin. It is commonly used as a biomarker to assess the presence of intravascular coagulation (Malaguarnera *et al.,* 2018).Coagulation causes the formation of the fibrin clot, while subsequent fibrinolytic system degradation produces a heterogeneous mixture of fibrin degradation products characterized by the presence of multiple D-dimer epitopes. D-dimer is a by-product of blood clotting and breakdown that can be detected by analyzing a blood sample (Bevan & Longstaff, 2022). D-dimer is released when a blood clot starts to disintegrate. A clot is formed by numerous platelets that are D-dimer bound together, along with additional components like fibrin (Bounds *et al.,* 2023). Venous thromboembolism (VTE) is not the only condition where elevated levels of D-dimer are seen; these levels are also seen in a number of other conditions where activation of coagulation and fibrinolysis takes place due to the significant number of comorbid conditions that have elevated d-dimer levels. An increased D-dimer level indicates hypercoagulability and secondary hyperfibrinolysis (Liang *et al.,* 2023).Anti-cardiolipin antibodies (ACA) are antibodies that are often against cardiolipin. They are a form of antimitochondrial antibody. Anti-mitochondrial antibodies, also known as autoantibodies, are immunoglobulins that have been formed against mitochondria, particularly the mitochondria of the cells in the liver. Antiphospholipid syndrome, syphilis and systemic lupus erythematosus (SLE) are among the clinical diseases where Anticardiolipin can be detected in detectable concentrations (Odewusi*et al.,* 2023). Anticardiolipin antibodies target M2 proteins, which are mitochondrial inner membrane proteins involved in energy metabolism and reactive oxygen species (ROS) production.Specifically, anticardiolipin antibodies binds to the M2 proteins in the mitochondria of endothelial cells, leading to mitochondrial dysfunction and reactive oxygen species (ROS) production (Becker *et al.,* 2019). They are produced by the immune system in response to an autoimmune reaction, which occurs when the body's immune system mistakenly targets and attacks its own tissues and cells. In the case of anticardiolipin antibodies, the immune system attacks cardiolipin, which can lead to clotting problems and an increased risk of developing thrombotic events, such as blood clots (Bustamante *et al.,* 2023). These complex autoantibodies are also linked to thrombosis (arterial and venous). The antibodies are more frequently found in patients without lupus and are paradoxically linked to recurrent abortion, neurological symptoms, myocardial infarction, unexplained venous and arterial thrombosis and myocardial infarction in young patients (Pignatelli *et al.,* 2020).

A vaccine is a preparation that contains weakened or inactive parts of a specific organism (antigen), which causes an immune response in the body. When vaccines are given into the human body, the immune system recognizes the antigens of the germs and produces antibodies against the pathogens, resulting in a powerful immunological response, this inhibits the pathogen from replicating after infection and hence the illness from developing (Ginglen & Doyle, 2023). Several types of COVID-19 have been produced including Pfizer-BioNTech and Moderna COVID-19 vaccines which are mRNA vaccines, Novavax COVID-19 vaccine which is a protein subunit vaccine and Johnson & Johnson's Janssen and Astrazeneca COVID-19 vaccines are viral vector vaccines. Disseminated intravascular coagulation (DIC) is characterized as a generalized hypercoagulable state that can cause microvascular and macrovascular clotting as well as impaired blood flow, which ultimately results in multiple organ dysfunction syndrome (Dhama *et al.,* 2020). Some studies have described the effect of COVID-19 vaccines on several biochemical and immunological parameters, but not much have been done on anticardiolipin antibodies and D-dimer. Therefore, the objective of this study was to evaluate serum anticardiolipin antibodies and D-dimer in recipients of COVID-19 vaccines in Ado-Ekiti, Ekiti State, Nigeria.

MATERIALS AND METHODS

Study design: This study was a case control design of recipients of COVID-19 vaccines in Ado-Ekiti State, Nigeria. The study involved young male and female adults aged 15-21 years.

Study area: The study was carried out at Ado-Ekiti and its environs. Ado-Ekiti is a town in Ekiti state in the southwestern part of Nigeria. The state is mainly and upland zone, rising over 250 meters above sea level. Its coordinates are 7° 40N' 5° 15E.

Sample size: The minimum sample size (N) was calculated by single proportion formula based on 2.2% estimated prevalence of COVID-19 disease. Allowance for error of 0.05 at 95% confidence interval (z) $N= Z^2p(1-p)/d^2$ (Araoye, 2004), Where; N= sample size; Z= control level at 95%; P= estimated percentage prevalence at 2.2%; d= margin of error at 0.05 (std). Substitute into formula gives equation 1:

$$N = \frac{1.96^2 * 0.22 * 0.98}{0.05^2} = 33.10 \quad (1)$$

A total of four-six (46) subjects were recruited for this study comprising of 16 fully vaccinated subjects, 15 partially vaccinated subjects and 15 unvaccinated subjects (control).

Inclusion criteria: Individuals who were fully and partially vaccinated against COVID-19 who gave their consent were included in this study.

Exclusion criteria: Subjects above 21 years of age, pregnant women, nursing mothers, Diabetes mellitus subjects and sufferers of autoimmune conditions were excluded from this study.

Ethical clearance: Ethical approval was obtained from the Health Research Ethics Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State. Informed consent was obtained from each subject who participated in the study.

Sample collection: Information on type of vaccine and dose of vaccine collected was obtained from subjects and documented. For each participant, 5ml of blood sample was collected by veinpuncture under aseptic conditions into a labeled dry, clean plain sample container. They were allowed to clot and centrifuged at 3,500 revolutions per minute for 5 minutes. After centrifuging, the serum was separated with the aid of a Pasture pipette and dispensed into dry chemically clean serum container, after which the samples were analyzed immediately or stored at -20^0C.

Analytical methods: Evaluation of anticardiolipin and D-dimer was done using Enzyme Linked Immunosorbent Assay (ELISA) (Elabscience Biotechnology Inc., USA).

Principle: ELISA is a plate-based assay technique designed for detecting and quantifying peptides, proteins, antibodies and hormones. In ELISA, an antigen must be immobilized to a solid surface and then complexed with an antibody that is linked to an enzyme. Detection is accomplished by assessing the conjugated enzyme activity via incubation with substrate to produce a measurable product. The most crucial element of the detection strategy is a highly specific antibody-antigen interaction.

Statistical analysis: The results were presented using tables and figures. Data was presented as mean ± S.D (standard deviation). Comparison was made between subjects and control groups using the student's t-test. Significant difference was accepted at $p<0.05$. All statistical analysis was done using SPSS version 25.0 software (SPSS Inc. Chicago, Illinois, USA).

RESULTS AND DISCUSSION

Table 1 showed the mean values of anticardiolipin antibodies and D-dimerin fully vaccinated subjects and control subjects. The result obtained showed that anticardiolipin and D-dimer were significantly higher ($p<0.0001$) in fully vaccinated subjects compared with the control subjects. Table 2 showed the mean values of anticardiolipin antibodies and D-dimer in partially vaccinated subjects and control subjects. The result showed that anticardiolipin and D-dimer were significantly higher ($p<0.0001$) in partially vaccinated subjects compared with the control subjects. Table 3 showed the mean values of anticardiolipin antibodies andD-dimerin fully vaccinated subjects and partial vaccinated subjects. The result obtained showed that anticardiolipin and D-dimer were insignificantly higher ($p>0.05$) in fully vaccinated subjects compared with partially vaccinated subjects.Figure 1 is a chart showing the mean values of D-dimer in fully and partially vaccinated subjects according to the different types of Coronavirus vaccines. From the results obtained, D-dimer was significantly higher in recipients of messenger RNA vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p<0.000$). No statistical significance difference was observed in D-dimer of recipients of viral vector vaccine when fully vaccinated subjects were compared with partially vaccinated subjects ($p=0.285$). There was significant difference in D-dimer of recipients of unspecified vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p=0.307$).

Figure 2 a chart showing the mean values anticardiolipin antibodies in fully and partially vaccinated subjects according to the different types of COVID-19 vaccines. The results obtained showed that anticardiolipin was significantly higher in recipients of messenger RNA COVID-19 vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p<0.000$). No significance difference was observed in anticardiolipin of recipients of viral vector vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p=0.316$). No statistical significant variation was

observed in anticardiolipin of recipients of unspecified vaccine in partially immunized subjects compared with fully immunized subjects (p=0.213).

Table 1. Mean values of anticardiolipin antibodies and D-dimerin fully vaccinated subjects and control subjects

Parameters	Fully Vaccinated (N=16)	Control Subjects (N=15)	p-value
D-Dimer (µg/ml)	3.37±1.12	1.34±0.78	0.0001
Anticardiolipin (µg/ml)	3.76±0.92	0.21±0.03	0.0001

Keys: N=number of subjects; Values are significant at p<0.05

Table 2. Mean values of anticardiolipin antibodies and D-dimer in partially vaccinated subjects and control subjects

Parameters	Partially Vaccinated (N=15)	Control Subjects (N=15)	p-value
D-Dimer (µg/ml)	2.99±1.18	1.34±0.78	0.0001
Anticardiolipin (µg/ml)	3.50±0.72	0.21±0.03	0.0001

Keys: N=number of subjects; Values are significant at p<0.05

Table 3. Mean values of anticardiolipin antibodies and D-dimer in fully and partially vaccinated subjects

Parameters	Fully Vaccinated (n=16)	Partially Vaccinated (n=15)	p-value
D-Dimer (µg/ml)	3.37±1.12	2.99±1.18	0.3652
Anticardiolipin (µg/ml)	3.76±0.92	3.50±0.72	0.3804

Keys: N=number of subjects, Values are significant at p<0.05

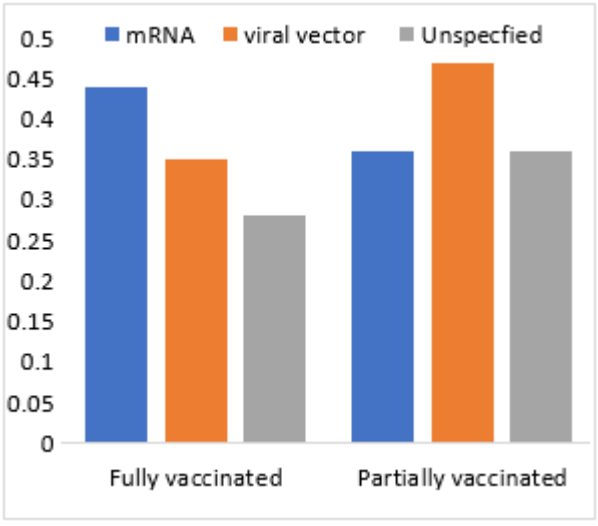

Fig 1. Chart showing mean values of D-dimer in fully and partially vaccinated subjects according to the different types of vaccines

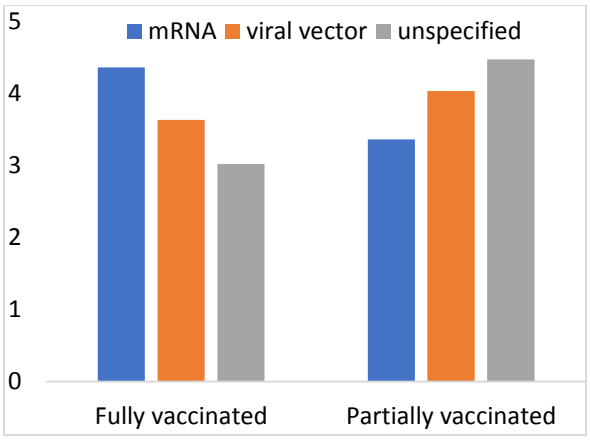

Fig 2. Chart showing mean values of anticardiolipin in fully and partially vaccinated subjects according to the different types of vaccines

Coronavirus disease 2019 (COVID-19) is a respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Lai *et al.*, 2020). It is associated with inflammatory responds which may lead to secretion of cytokines resulting to cytokines storm leading to formation of blot clots characterized with varying complications such as renal and hepatic impairment, stroke, diastolic cardiac dysfunction and pulmonary hypertension (Batta *et al.*, 2022). To curb the menace of coronavirus, vaccines were produced (messenger RNA vaccines, protein subunit vaccines, viral vector vaccines). As the components or parts of the virus was incorporated into the vaccine, coupled with the fact that the trial time of the vaccines was initially short, resulting in public concerns about the safety of the vaccines, this research was designed to find out whether autoimmunity and intravascular coagulation are also consequences of the vaccines.

In this study, D-dimer was found to be significantly higher in fully and partially vaccinated COVID-19 subjects compared to control (p<0.05). D-dimer is generated in the blood by the degradation of stabilized fibrin polymer by plasmin and is degraded again by the activation of fibrinolysis. The underlying pathophysiology leading to a hypercoagulable state may be related to a cytokine storm causing endothelial damage, microvascular thrombosis, and/or the development of prothrombotic antiphospholipid antibodies (Emert *et al.*, 2020; Meisinger *et al.*, 2022). The pathophysiologic mechanism underlying COVID vaccine is not clear, but studies suggest that activation of the coagulation pathway, fibrinolysis, and pulmonary microvascular immunothrombosis may play a role during the onset of COVID-19 infection (Kalaivani & Dinakar, 2022). This finding is in agreement with previous studies (Meisinger *et al.*,

2022; Kalaivani & Dinakar, 2022; Bikdeli *et al.,* 2022) in which elevated D-dimer in COVID-19 infection and vaccination have been reported.

The result of this study revealed that there was no significant difference in D-dimer of fully vaccinated subjects compared to partially vaccinated subjects ($p>0.05$). This is as a result of impaired disseminated intravascular coagulation after administering the first dose of the vaccine. The incorporation of one, two or more viral components into the COVID-19 vaccines, upon entering the system triggers immune response resulting to over secretion of cytokines known as cytokine storm and other inflammatory process, thereby resulting to intravascular coagulation (Savla *et al.,* 2021).Furthermore, D-dimer was significantly higher in recipients of messenger RNA vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p<0.05$). Fazio *et al.* (2022) reported that mRNA vaccines could determine micro and macro thrombosis, because a significant elevation of D-dimer was found in a certain percentage of subjects who were vaccinated for COVID-19 with any type of vaccine. In addition to the autoimmune mechanisms induced by adenovirus vaccines, it has been hypothesized that the spike protein itself could directly damage the endothelial cells and can bind to platelet angiotensin converting enzyme-2 (ACE-2) receptor enhancing platelets aggregation and thrombosis (Zhang *et al.*, 2020).

In this study, anticardiolipin was significantly higher in fully and partially vaccinated subjects compared to control ($p<0.05$). This could be due to the introduction of few SARS CoV-2 viral components in the COVID-19 vaccine resulting in an antiphospholipid syndrome characterized by the formation of blot clot. Production of antiphospholipid antibodies is common after viral infections. Some patients may have these antibodies for short period of time, yet in some cases they persist and can contribute to the development of autoimmune diseases (Serrano *et al.,* 2022).Antibodies called anti-cardiolipin antibodies (ACA) are directed against cardiolipin, a crucial component of the inner mitochondrial membrane that makes up around 20% of the membrane's total lipid content. Immunocompromised individuals (such as COVID-19 patients) frequently have ACA, in which self-antibodies kill self-antigens (Odewusi *et al.,* 2023). This finding agrees with previous study in which autoimmunity was significantly higher in recipients of the COVID-19 vaccines (Krashias *et al.,* 2022; Serrano *et al.*, 2022).

In this study, there was no significant difference in anticardiolipin of fully vaccinated subjects compared to partially vaccinated subjects ($p>0.05$). Elevated anticardiolipin antibodies, a susceptibility to the antiphospholipid syndrome may be a complication of COVID-19 vaccine which may also be the reason why there is higher likelihood of intravascular coagulation in recipients of COVID-19 vaccine. The antiphospholipid syndrome is an autoimmune hypercoagulable state that can result in thrombotic events such as deep venous thrombosis, pulmonary embolus, and stroke (Cimolai, 2021). Furthermore, anticardiolipin was significantly higher in recipients of mRNA COVID-19 vaccine in fully vaccinated subjects compared with partially vaccinated subjects ($p<0.05$). Unlike other types of vaccine, mRNA can serve as an adjuvant and an immunogen (encoding the viral protein) because of its inherent immunostimulatory properties. Type I interferon and other inflammatory cytokines are produced as a result of the intrinsic adjuvant activity of the vaccinations, which also activates innate sensors (Teijaro *et al.,* 2021). There have been several reports of thrombotic adverse events after administration of the mRNA COVID vaccine (Jabagi*et al.,* 2022). The onset of autoimmune disease has also been reported following viral illness as well as following vaccination (Talotta *et al.,* 2021).

Conclusion: The significant increase in D-dimer and anticardiolipinin recipients of COVID-19 vaccines means that among recipients of COVID-19 vaccines, early detection and treatment of disseminated intravascular coagulation is critical for survival. Elevated anticardiolipin levels which could be responsible for intravascular coagulation in Coronavirus vaccine recipients may be useful to prevent serious cases of coagulation following vaccination. Healthcare providers should be aware of clinical presentation and management strategies associated with post COVID-19 vaccine-induced autoimmunity and intravascular coagulation.

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