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Assessment of Serum Levels of Immunoglobulin A (IgA) Class in Patients with COVID-19 and Asthma

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Authors' contributions

This work was carried out in collaboration among all authors. Author GOA designed the study design, analyzed and interpreted the patient data, and drafted and wrote the manuscript. Authors IA and ZBF performed the laboratory analysis and revised the manuscript. Author AK enrolled the patient and collected of the data. Author AAB participated in the paper drafting and study design. The authors read and approved the final manuscript.

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ABSTRACT

Background: Growing interest in the importance of the mucosal immune system, coupled with an improved understanding of the functional properties of IgA has re-engineered interest in this previously neglected immunoglobulin class. Research into IgA roles and levels might open a novel approach in therapeutic settings and mucosal vaccination. Both COVID-19 and asthma are broncho-mucosal inflammatory diseases. However, the exact role or levels of IgA during the pathogenesis of these diseases is unclear.

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Objective: To investigate the levels of IgA as a potential differentiating biomarker of patients with COVID-9 or asthma from controls.
Methodology: Serum IgA levels were measured in 30 patients with bronchial asthma and 30 COVID-19 patients with their 30 corresponding age- and sex-matched healthy control subjects using enzyme-linked immunosorbent assay.
Results: The mean value of serum IgA was significantly increased in COVID-19 patients at admission (p=0.001) or COVID-19 patients at discharge (p=0.031) compared with the level in corresponding control. The mean value of serum IgA was similar in COVID-19 patients at admission compared with COVID-19 patients at discharge. The mean values of serum IgA were not significantly higher in COVID-19 patients at admission and COVID-19 patients at discharge compared with asthma patients (p>0.50). The mean value of plasma IgA was significantly decreased (p=0.018) in asthma patients compared with the level in corresponding control.
Conclusions: Serum IgA could be a useful biomarker to differentiate patients with COVID-9 or patients with asthma from un-infected controls.

Keywords: Adaptive immunity; immunoglobulin A class; lung diseases.

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019
DC : Dendritic cells
ELISA : Enzyme-linked immunosorbent assay
HRP : Histidine-Rich Protein
IDC : Infectious Diseases Center
IDO : Indoleamine-2, 3-dioxygenase enzyme
IFN : Interferon
IgA : Immunoglobulin class A
IgE : Immunoglobulin class E
IL 2, 4 : Interleukin 2, 4
LPS : Lipopolysaccharide
MISC-C: Multisystem Inflammatory Syndrome in COVID-19
O.D : Optical density
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
TLR : Toll-like receptors
UI/UCH: University of Ibadan/University College Hospital

1. INTRODUCTION

Understanding the mechanisms of diseases could lead to the development of highly specific methods of treatment. However, the exact etiology of COVID-19 and asthma is yet not been fully clarified [1]. IgA is an abundant immunoglobulin classes secreted into external fluids and binds various receptors of immune cells as first described in 1953 [2]. These cells are particularly important in the pathogenesis of COVID-19 and asthma. In the serum, IgA exists as a monomer, however, it elicits its diverse functions at the mucosal level as a dimeric secretory IgA (s-IgA) [3]. The luminal epithelium is always exposed to exogenous antigens. These antigens are endocytosed by subepithelial antigen-presenting cells (APC), processed and presentated to immune cells in the nasopharynx, across the nasal epithelium and tonsils and adenoids [4]. Thus, it is important to determine the levels of IgA during respiratory diseases, but this is grossly understudied.

Asthma is a chronic inflammatory disease of the airways with intricate and complex pathophysiologyinvolving airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness initiated by IgE antibodies and non-IgE factors [5] which respond to certain triggers in the environment and bind to high-affinity mast cells and basophils. This results in the degranulation of the inflammatory cells with subsequent release of histamine, prostaglandins, leukotrienes and cytokines thereby causing inflammation and bronchoconstriction with its associated intermittent airflow obstruction, resulting in increased difficulty in breathing. Reports have shown that there is an association between asthma and impaired innate or

adaptive immunity or the existence of selective IgA deficiency (sIgAD) [6]. IgE is the most studied immunoglobulin class in patients with asthma [7], neglecting bronchial-associated immunoglobulin (IgA).

The emergence of global pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had devastating implications on health and socioeconomic activities [8]. Studies have shown that IgA produced in the bronchial-associated lymphoid tissue served as the main line of humoral defense against SARS-CoV-2 after its entry and subsequent internalization of angiotensin-converting enzyme 2 receptors [9,10]. During the early period of infection, SARS-CoV-2 spike protein specific IgA has been shown to be the foremost response against the virus [11]. IgA is a potent anti-viral antibody against virus-infected epithelial cells and it is effective in re-directing antigens to the lumen when they enter the lamina propria [12]. Its potency against upper airway viral infections such as rhinovirus, [13] influenza, [14] and SARS-CoV-2 [15] has been demonstrated by its increase of infected patients [14]. Experimental studies have also shown that transfer of nasal IgA from immunized to naïve mice leads was protective against influenza infection. [16] Studies have also shown that intranasal challenges by influenza results in increased viral load in mice lacking S-IgA [17]. Present, there is no information on the changes in the serum levels of IgA during the course of COVID-19 management.

This study was designed to determine if serum levels of IgA could be used to differentiate or prognosticate patients with lung diseases such as COVID-19 or asthma. The outcome could be applied in the suggestion for the use of IgA strategy in the treatment of lung mucosal diseases.

2. METHODOLOGY

2.1 Study Design and Laboratory Procedures

The study was a case–control study which included 90 subjects recruited from University College Hospital, Ibadan, and Infectious Diseases Center (IDC), Olodo, Ibadan, Nigeria. The study population was 30 newly diagnosed asthma patients with 30 corresponding control (aged 15-20yrs) and 30 newly diagnosed COVID-19 patients followed up till discharge compared with 30 corresponding control (aged 12-36yrs). Patients with COVID-19 were follow-up till discharged from the isolation centerr. SARS-CoV-2 infection was confirmed in the patients using real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay in nasal and pharyngeal swab specimens [18]. Patients with asthma as per the definition of the American Thoracic Society [19] were chosen for the study. They were newly diagnosed at the Medical Outpatient Clinic, University College Hospital, Ibadan, Nigeria. Control were recruited from staff and students from University of Ibadan, Nigeria who were confirmed not having SARS-CoV-2 infection or asthma using clinical and laboratory investigations as confirmed by consultant physicians. Individuals on medication (antihistamines, steroids, and compulsory drugs) and those with skin disorders or dermatographia were excluded. None of the subjects was pregnant or had co-existing diseases like diabetes, cardiac disease, renal and/or liver dysfunction.

Venous blood sample (5ml) was collected from each study participants abd dispense into plain tubes to obtain serum which were frozen and stored at -20^{o}C intil analysis was performed. Samples were analyzed for the levels of IgA using ELISA following manufacturer instruction (Elabscience, USA).

2.2 Statistical Analysis

Data were analyzed using the SPSS statistical software, version 23.0. Results were presented as mean (±SD). Differences in the mean (±SD) of the parameters were determined the Student t-test. *p*-values less than 0.05 were considered as statistically significant.

3. RESULTS

The mean value of serum IgA was significantly increased in COVID-19 patients at admission ($p<0.001$) or COVID-19 patients at discharge ($p<0.031$) compared with the level in the control. See Tables 1 and 2. The mean value of serum IgA was similar in COVID-19 patients at admission compared with COVID-19 patients at discharge ($p>0.50$). See Table 3. The mean value of plasma IgA was significantly decreased ($p=0.018$) in asthma patients compared with the level in the control (Table 4). The mean values of serum IgA were not significantly higher in COVID-19 patients at admission and COVID-19

patients at discharge compared with asthma patients (p>0.50). See Table 5. None of the participants have IgA values outside the normal reference values (70-400mg/dL). See Table 6.

Table 1. The mean level of IgA (mg/dL) in COVID-19 patients at admission compared with control

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at admission	30	250	40.00		
Controls	30	245	59.00	3.40	<0.001

Table 2. The mean level of IgA (mg/dL) in COVID-19 patients at discharge compared with control

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at discharge	30	251	61.00		
Controls	30	245	59.00	2.25	<0.031

Table 3. The mean level of IgA (mg/dL) in COVID-19 patients at admission compared with COVID-19 patients at discharge

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at admission	30	250	40.00		
COVID-19 patients at discharge	30	251	61.00	0.088	>0.50

Table 4. The mean level of IgA (mg/dL) in COVID-19 patients in asthmatic patients compared with control

Groups	N	Mean	SD	t-value	P-value
Asthma	30	248	40.00		
Controls	30	255	20.00	4.37	<0.018

Table 5. The mean level of IgA (mg/dL) in COVID-19 patients at admission and COVID-19 patients at discharge compared with asthma patients

Groups	N	Mean	SD	t-values	P-values
COVID-19 patients at admission	30	250	40.00		
COVID-19 patients at discharge	30	251	61.00		
Asthma	30	248	40.00		
t-value, P-value[a]				0.20	>0.05
t-value, P-value[b]				0.23	>0.50

[a]*COVID-19 patients at admission compared with asthma patients*
[b]*COVID-19 patients at discharge compared with asthma patients*

Table 6. Frequency of COVID-19 patients or asthma patients or control having IgA values outside the normal reference ranges (70-400mg/dL)

Groups	% of participants having IgA values outside the normal reference ranges
Asthma	0%
COVID-19	0%
Control	0%

4. DISCUSSION

Unlike in gastrointestinal diseases, the role of IgA in airway disease are basically understudied. Available reports on function of IgA in airway diseases were largely determined in patients with chronic obstructive pulmonary disease (COPD), [20] asthma, [20] and cystic fibrosis [21]. Reports have shown that respiratory infections, allergies, and auto-immune diseases are commoner in patients with secretory IgA deficiency compared with individuals without the deficiency [22,23]. The current study has provided information on the serum IgA levels in two different lung mucosal diseases (COVID-19 and asthma). Results from this study showed that there was a statistically significant decrease in serum IgA in the asthma patients than in the corresponding control patients. This observation supports previous findings [24-26]. Reduced IgA in asthmatic patients might explain the increased risks of bacterial infections in them [24]. A studies earlier suggested that asthma is associated with existence of selective IgA deficiency (sIgAD) [6]. Asthma patients on treatment were excluded from this study because serum IgA level was reported to be significantly lower among asthma patients using inhaled corticosteroids [27].

Asthma, a disease of the airways of no fixed etiology is known to involve eosinophil degranulation, cytokine secretion, and raised level of IgE [7] but the involvement of IgA in asthma pathophysiology is largely unknown. Previous study suggested that IgA participates in eosinophil degranulation in patients with atopic asthma [28]. Furthermore, IgA facilitates the phagocytosis of antigens due to the presence of specific IgA Fc receptors [29]. Studies have also shown that IgA plays a role in the pathogenesis of IgA nephropathy as deposits of IgA together with Complement components have been reported in the mesangial area of the kidney [30]. Experimental studies have also shown that IgA is involved in the asthma-associated lung injury as deposits of IgA immune complexes were observed in lungs of rats [31]. These properties of IgA explains its role in inflammation [29]. These support the consumption of IgA in asthma patients, thus its reduced mean level compared with corresponding control.

Several cell types bind IgA as depicted by the presence of prototype Fc receptor for IgA FcαRI (CD89) on neutrophils, eosinophils, monocytes, and macrophages [29]. This results in activation of a myriads of effector activitiess in asthmatics. These effector activities includes phagocytosis, production of reactive oxygen intermediates, degranulation, and production of cytokines [32-37]. Reports have shown that the levels of IgA in broncho-alveolar fluid and sputum from patients with asthma are higher than those in controls.[28] Also, complexes of IgA and IL-8 have been detected in induced sputum, and the levels of these complexes were higher in atopic asthmatics compared with that in non-atopic control participants [38]. Increased leakage of IgA from the circulation is considered one of the mechanisms responsible for increased IgA in pulmonary secretions. Evidence abound from *in vitro* studies that the transport of IgA across the epithelium may be enhanced by cytokines. Synergistic effects of IL-4 and interferon (IFN)-gamma synergistically enhance the expression of secretory components and binding of IgA to cultured epithelial cells thereby increasing the secretory component mediated transport of IgA across the epithelium [39,40]. All these mechanisms might explain the decreased level of serum IgA found in our asthmatics compared with controls.

Reports have shown that there is marked elevation of total IgA in severe SARS-CoV-2 infection [11,15]. These reports ahowed that there is stimulation of a strong IgA-driven immune response in the bronchial-associated lymphoid tissue when SARS-CoV-2 infects and persists in the respiratory system [41]. This probably explain our observed elevated levels of IgA in COVID-19 patients at admission and discharge compared with controls or similar levels of IgA in COVID-19 patients at admission compared with COVID-19 patients at discharge. Studies have shown a link between IgA and multisystem inflammatory syndrome in COVID-19 (MIS-C), which is a novel COVID-19–related disease [42,43]. Our present study, therefore, suggests that elevated total IgA might have a causal role in MIS-C.

The role of IgA in asthma has been less explored. Low serum IgA levels in asthmatics have been associated with recurrent infections. [24], Similarly, individuals with IgA-deficiency have been reported to be at high risk of developing autoimmune disease of the gastrointestinal tract, as about 1% of individuals with coeliac disease are IgA-deficient [41]. It could therefore be hypothesized from our study that low IgA level in asthma patients might be responsible for the future occurrence of recurrent

infection and autoimmune disorders in them. The determination of levels and prevalence of autoantibodies may be carried out in asthma patients to establish the linkage of autoimmunity and asthma episode. However, none of the participants had serum IgA level below or avove the normal reference range (70-400mg/dL). Binding of IgA to myeloid-cell-specific type I Fc receptor for IgA (FcαRI or CD89), the Fcα/Fcμ receptor, the asialoglycoprotein receptor, and the transferrin receptor [44] results in both pro-inflammatory or anti-inflammatory pathways. Binding of monomeric IgA to FcαRI results in anti-inflammatory process whereas, IgA immune complexes results in FcαRI-dependent pro-inflammation [45]. Thus, the observed elevated level of monomeric serum IgA in COVID-19 might be a strategy to produce anti-inflammatory signals through binding with FcαRI to dampen excessive inflammation in COVID-19 patients.

Production of IgA is largely in response to transforming growth factor-β1 (TGFβ1), that activates the specific promoters responsible for class switching to IgA. Reports have also shown B-cell activation in combination with other cytokines, such as interleukin-2 (IL-2), IL-4, IL-5, IL-6, and IL-10 can result in IgA switching [46,47]. These cytokines have been reported to elevated during episodes of “cytokine storm”in COVID-19 patients, thereby resulting in increased level of IgA as reported in this study. Reports have also shown that binding of lipopolysaccharide (LPS) to Toll-like receptors (TLRs) or polysaccharides to the B-cell receptor results in a T-cell independent production of non-specific, polyreactive IgA via direct activation of B cells or induction of a selective IgA class switch in B cells [48]. LPS, TLR, and polysaccharides are increased in COVID-19 patients [49] which might stimulate the production of polyreactive IgA [50] and recognise plethora of antigens thereby providing lilited protection against multiple pathogens [51]. The observed elevated IgA level in COVID-19 patients might therefore be another protective advantage for these patients. IgA has also been found to be elevated following vaccination against SARS-CoV-2 in a cohort of high-risk first responders [51]. Ideally, this is another support for the protective role of IgA during SARS-CoV-2 infection and vaccination.

None of the participants had serum IgA levels outside the normal reference range (70-400mg/dL). This might explain non-significantly raised mean level of IgA in COVID-19 patients relative to asthma patients. The opposite directions of mean IgA levels in each disease condidtion relative to the corresponding controls might support differential causes and pathogenencities of COVID-19 and asthma, aside form the fact that asthma has multifactorial initiators [5]. The main limitation of the current study was the small size of its sample. Hence, it is recommended for future research to conduct larger studies to include COVID-19 patients who are of similar ages and gender with asthma patients. Nevertheless, the inclusions of extensive exclusion criteria are the major strength of this study.

5. CONCLUSION

It could be concluded from this study that a robust antiviral IgA response is triggered in patients with COVID-19. Also and that significantly raised mean IgA level in COVID-19 patients and significantly reduced mean IgA level in asthma patients compared with their corresponding controls differentiate COVID-19 patients or asthma patients from control. This is a similar trend to a recent report from our laboratory using activities of plasma indoleamine-2, 3-dioxygenase enzyme (IDO) in patients with asthma, pulmonary tuberculosis, and COVID-19 [52]. Observations from this present study highlight the protective roles of IgA in COVID-19 patients and that IgA might be one of the neutralising antibodies stimulated by CPVID-19 vaccines. However, non-significant difference in mean IgA level of COVID-19 patients compared with asthma patients call for further study on larger cohorts of matched age and gender.

The major importance of the present study is that IgA is protective in COVID-19 patients and that IgA might be one of the neutralizing antibodies stimulated by COVID-19 vaccines. However, IgA contributed to the pathology of lung injury in asthma patients.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

CONSENT AND ETHICS APPROVAL

Ethical approval from Institutional Ethics Committee (Approval number: UI/EC/20/0283) and consent from participants or relatives to participate were obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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