

Assessment of serum levels of immunoglobulin A (IgA) class in patients with COVID-19 and asthma

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.

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.

INTRODUCTION

A deeper understanding of 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 one of the most abundant immunoglobulin classes secreted into external fluids and binds various receptors on granulocytes, monocytes, macrophages, dendritic cells (DC), and eosinophils, as it was first described in 1953.[2] These cells are particularly important in the pathogenesis of COVID-19 and asthma. Although IgA is present in the serum as a monomer, its main known functions are elicited at

the mucosal level in the form of dimeric secretory IgA (s-IgA).[3] The luminal epithelium is continuously exposed to exogenous antigens, which are endocytosed by subepithelial antigen-presenting cells (APC) for processing and presentation to immune cells in the nasopharynx, across the nasal epithelium and tonsils and adenoids (Waldeyer's ring).[4] Thus, it is important to determine the levels of IgA during respiratory diseases, but this is grossly understudied.

Asthma is a chronic inflammatory condition of the airways with intricate and complex pathophysiology involving 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. Inhaled pollutant or risk factor causes mast cell degranulation, the release of cytokines histamine, prostaglandins, and leukotrienes. As a result of inflammation and bronchoconstriction, there is an intermittent airflow obstruction, resulting in increased difficulty in breathing. Studies suggested that asthma is associated with impaired innate and 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 novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a global pandemic with wide-ranging health and socioeconomic implications.[8] SARS-CoV-2 enters human cells by attachment to and subsequent internalization of angiotensin-converting enzyme 2 receptors that are highly expressed by Type II pneumocytes in the deep bronchial system,[9] where immunoglobulin (Ig) A, produced in the bronchial-associated lymphoid tissue, is the main line of humoral defense.[10] Indeed, specific IgA production against the SARS-CoV-2 spike protein has been shown to appear early in infected patients.[11] However, despite the important role of IgA in mucosal immunity, the level of total IgA generated in response to SARS-CoV-2 infection remain unexplored. IgA is very effective at tackling viruses in virus-infected epithelial cells and in redirecting antigens to the lumen when they enter the lamina propria.[12] Upper airway infection with certain viruses such as rhinovirus,[13] influenza,[14] and SARS-CoV-2 [15] has shown to induce an increase of IgA in the nasal lavage and for influenza, playing an important role in the protection against viral infection in humans.[14] This is supported by murine studies where transfer of nasal IgA from immunized to naïve mice leads to protection against influenza infection [16] and mice lacking S-IgA have increased viral load after

intranasal challenges.[17] No articles are currently discussing the role of IgA in COVID-19 patients at admission and discharge.

This study aimed to explore whether 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 the IgA strategy in the treatment of lung mucosal diseases.

METHODOLOGY

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

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). COVID-19 patients recruited from IDC, Olodo, were enrolled in this study. The COVID-19 cases were confirmed by detection of hCoV nucleic acid using real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay in nasal and pharyngeal swab specimens following recommended guidelines apart from clinical signs of dry cough, high fever, sore throat and shortness of breath.[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. Subjects 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.

Other exclusion criteria were smoking, subjects with secondary immune deficiency, diabetes hypertension, and malignancy or subjects taking medications including antiepileptics sulfasalazine, D penicillamine, thyroxine, captopril, levamisole, systemic corticosteroids, and cyclosporine or history of immunosuppressive medications and co-morbid conditions such as rheumatoid arthritis, lupus, celiac disease, or inflammatory bowel disease to avoid the confounding effect. Whole blood collected into a plain tube was allowed to clot and retract before being spun at 2,000 x g for 10 minutes for the collection of serum. The serum was stored at -20⁰C until analyzed.

Venous blood samples were collected from all subjects in 5ml vacutainer tubes without anticoagulants. All samples were processed at the Department of Immunology laboratory at the College of Medicine, University of Ibadan, Nigeria. Serum samples were frozen and stored at -80⁰C until analysis was performed. Samples were analyzed for the levels of IgA using based on the method described by the manufacturer (Elabscience, USA, Catalogue number E-EL-H6071) as follows: 50µl per well of appropriate sample dilution buffer, antigen standard cocktail or experimental sample was pipetted into microtiter plates. This was incubated at room temperature (27°C). The ELISA immunoplate was washed 3 times with 350µl/well of washing buffer. 100µl per well of detection antibodies was added. This was incubated at room temperature for 60 minutes. The immunoplate was re-washed 3 times with 350µl/well of washing buffer. 100µl/well of diluted Avidin-HRP conjugate was added, after which the plate was incubated at room temperature for 30 minutes avoiding light rays. The plate was washed 4 times and 100µl per well of developing solution was added. The reaction was stopped with 100µl/well of Stop Solution and absorbance optical density (O.D) was read at 450nm within 30 minutes following the addition of stop solution. The average absorbance value of each O.D. was plotted against corresponding cytokine values to plot a standard curve. The average absorbance of each serum sample was used to determine corresponding cytokine values by interpolating from the curve.

Statistical Analysis: Data were analyzed using SPSS and the values were presented as mean (±SD). Mean (±SD) between and within the two groups were compared using the Student t-test. *Ap*-value ≤0.05 was reported as significant.

RESULTS

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

^aCOVID-19 patients at admission compared with asthma patients

^bCOVID-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%

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.

DISCUSSION

Unlike in gastrointestinal diseases, the role of IgA in airway disease remains largely understudied. The reported function of IgA was determined in chronic obstructive pulmonary disease (COPD),[20] asthma,[20] and cystic fibrosis.[21] Moreso, patients with secretory IgA deficiency seemed to present with more frequent respiratory infections, allergies, and autoimmune diseases compared to patients with normal IgA levels.[22, 23] The current study has provided information concerning serum IgA levels in two lung mucosal diseases (COVID-19 and asthma). Based on the results of this study, it was found that there was a statistically significant decrease in serum IgA in the asthma patients than in the corresponding control patients. This supported previous findings.[24, 25, 26] Reduced IgA in asthmatic patients might be the reason for 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. A previous study suggested the participation of IgA 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] Also, the role of IgA in the pathogenesis of IgA nephropathy has been extensively studied, and deposits of IgA together with Complement components are observed in the mesangial area of the kidney.[30] IgA might be the cause of lung injury in asthmatics, as shown by the presence of IgA immune complex-mediated acute lung injury in rats.[31] The capacity of IgA to trigger the release of mediators from inflammatory cells and to activate the Complement System explains IgA's role in inflammation.[29] These support the consumption of IgA in asthma patients, thus its reduced mean level compared with corresponding control.

Various cell types have been found to bind IgA as depicted by the presence of prototype Fc receptor for IgA Fc α RI (CD89) on neutrophils, eosinophils, monocytes, and macrophages.[29] This leads to the activation of a variety of effector functions in asthmatics, including phagocytosis, production of reactive oxygen intermediates, degranulation, and production of cytokines.[32-37] Moreover, the levels of IgA in broncho-alveolar fluid and sputum from patients with asthma are higher than those in controls.[28] In addition, 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 healthy non-atopic control participants.[38] Increased IgA levels in pulmonary secretions can be explained by increased leakage of IgA from the circulation among other mechanisms. There is evidence from *in vitro* studies that cytokines implicated in the pathogenesis of asthma may enhance the transport of IgA across the epithelium. IL-4 and interferon (IFN)-gamma synergistically enhance the expression of secretory components and binding of IgA to cultured epithelial cells.[39] In line with this observation, IFN-gamma and IL-4 were found to increase secretory component-mediated transport of IgA across epithelium in cell culture.[40] All these mechanisms might explain the decreased level of serum IgA found in our asthmatics compared with controls.

In this study, we measured total IgA in COVID-19 patients at admission or discharge compared with control of similar ages and gender. A previous finding showed a marked elevation of total IgA in severe SARS-CoV-2 infection.[11, 15] These data support our hypothesis that a strong IgA-driven immune response was stimulated in the bronchial-

associated lymphoid tissue when SARS-CoV-2 infects and persists in the respiratory system.[41] Thus explaining our findings of raised 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. Data supported 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. A study linked significantly lower serum IgA levels in asthmatics with recurrent infections,[24], and it was well documented that IgA-deficient individuals have an increased incidence of autoimmune disease of the gastrointestinal tract. About 1% of individuals with coeliac disease were IgA-deficient.[41] The authors of the present study hypothesized that reduced IgA in asthma patients might be liable 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.

Binding of IgA to myeloid-cell-specific type I Fc receptor for IgA (Fc α RI or CD89), the Fc α /Fc μ receptor, the asialoglycoprotein receptor, and the transferrin receptor[44] results in both pro-inflammatory as well anti-inflammatory pathways. Anti-inflammatory signals are generated by Fc α RI upon binding of monomeric IgA, whereas pro-inflammatory Fc α RI-dependent responses are induced by IgA immune complexes.[45] Thus, raised monomeric serum IgA in COVID-19 patients might be a strategy to produce anti-inflammatory signals through binding with Fc α RI to dampen excessive inflammation in COVID-19 patients.

IgA production typically occurs in response to transforming growth factor- β 1 (TGF β 1), which activates the specific promoters responsible for IgA class switching. It has been described that IgA switching can also occur through B-cell activation in combination with other cytokines, such as interleukin-2 (IL-2), IL-4, IL-5, IL-6, and IL-10.[46, 47] These cytokines have been reported to raised during episodes of “cytokine storm” in COVID-19 patients, thus an increased level of IgA is expected and as reported in this study. Also, lipopolysaccharide (LPS) via Toll-like receptors (TLRs) or polysaccharides through the B-cell receptor produce non-specific, polyreactive IgA in a T-cell independent way by directly activating B cells or induce 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]. These polyreactive antibodies recognize multiple antigens and are therefore able to provide limited protection against a plethora of pathogens.[51] Therefore, increased IgA in COVID-19 patients might be another protective advantage for these patients. In support of its role as a neutralizing antibody that excludes antigens, 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.

However, none of the participants had serum IgA levels below or above 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 condition relative to the corresponding controls might support differential causes and pathogenicities of COVID-19 and asthma, aside from 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.

Conclusion

This novel data concluded that a vigorous antiviral IgA response was triggered in the bronchial mucosa of COVID-19 patients 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] 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.

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

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

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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