Italian Journal of
Gynæcology & Obstetrics
June 2026 - Vol. 38 - N. 2 - Quarterly - ISSN 2385 – 0868

Potential association of anti-gliadin antibodies (IgA and IgG) levels with vulvovaginal candidiasis: a case-control study

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ARTICLE INFO

History
Received: 11 June 2025
Received in revised form: 08 July 2025
Accepted: 02 October 2025
Available online: 22 June 2026

DOI: 10.36129/jog.2025.245

Key words
Candida; vulvovaginal candidiasis; gliadin; IgA AGA; IgG AGA.

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ABSTRACT

Objective. Anti-gliadin antibodies (AGA) detection is a former diagnostic test for celiac disease (CD). This study aimed to determine whether vulvovaginal candidiasis (VVC) can induce AGA production and the significance of AGA in the diagnosis of this disease.

Materials and Methods. A case-control study was conducted to consist of 90 subjects in two groups: 50 VVC patients and 40 women without VVC. Swabs were collected from all subjects to diagnose VVC. Serum was analysed to detect AGA by ELISA assay.

Results. Levels of IgG AGA were normal in both groups. Eleven patients had elevated IgA AGA levels. Of the 11 patients, four were very positive (4%), and seven had moderate increases in antibody levels (14%). IgA AGA showed 84.76% sensitivity and 90% specificity. The diagnostic cutoff value of IgA AGA for VVC is at 20 U/ml.

Conclusions. The low number of positive IgG-AGA detected in the VVC patients suggests that using this immunomarker as a diagnostic tool for this fungal infection needs more confirmation and it's too early to establish a strong correlation between VVC and AGA levels. Confirming such correlation may help differentiate fungal infection in the vagina from the same clinical features caused by other organisms.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is an infection of high prevalence and incidence in women around the world caused by the pathogenic activity of *Candida* species [1]. *C. albicans* is the most common species of *Candida* causing VVC which can affect women of all ages [2]. This type of fungi lives as a member of the normal flora of the vagina and can become pathogenic under particular circumstances [1]. Anti-gliadin antibodies (AGA) with its two classes, IgA and IgG, are mainly used in the diagnosis of celiac disease (CD) [3]. This test has become insignificant since it was found that the production of anti-gliadin antibodies is not specific to CD and can be produced in response to other diseases [4]. AGA levels may be elevated in healthy individuals or patients with diseases other than CD such as psoriasis, hepatic disorder, rheumatoid arthritis, nephritis, thyroid disorders,

sickle-cell anaemia, and other intestinal tract disorders [3, 4].

Numerous studies indicate a possible correlation between *Candida* spp. and CD [5-7]. This correlation is based on the sharing of many pathophysiological features such as the production of AGA and anti-tissue transglutaminase (anti-tTG) antibodies [5, 6]. *C. albicans* has a specific protein within its cell wall, Hwp1, which has similar amino acid sequences to the gliadin protein and has the ability to stimulate the production of AGA [7]. This study is designed based on the assumption that the ability of heavy growth of *Candida* to stimulate the production of AGA can be useful in using AGA as an indicator for the diagnosis of candidiasis. The basis for this assumption is two cases of patients with cutaneous candidiasis who did not have CD [8, 9]. These cases showed that two patients with chronic mucocutaneous candidiasis had elevated levels of AGA. Because of this, assessing the capacity of a particular type of candidiasis, VVC, to stimulate production of AGA is main goal of this study.

MATERIALS AND METHODS

Patients

A total of 90 participants, including 50 VVC-positive patients (age range: 16-57 years) and 40 women without VVC as a control group (age range: 20-30 years), were included in the case-control study. Subjects attended AL-Zahraa hospitals in AL-Najaf province of Iraq from November 2020 to February 2021. Vulvovaginal Candidiasis (VVC) was clinically diagnosed in the patient group by the gynaecological consultant of the hospital as the first step. VVC is characterized by vaginal discharge that is foamy or cheese-like, with vulvar itching, pain, and sometimes dysuria or dyspareunia [1, 2]. Patients with history of any autoimmune diseases such as CD, rheumatoid arthritis or type 1 diabetes, those under hormone treatment and with other diseases that can increase AGA levels such as psoriasis, endocrine disorders, urinary system disorders and gastrointestinal problems were excluded from this study.

Collection and processing of vaginal samples

Double swabs of the vaginal area were taken from each subject. One swab sample was microscopically examined with Gram staining to determine the morphology of *Candida* species. Another swab was cultured on Sabouraud's Dextrose agar (SDA) (Hi-Media, India). Inoculated plates were incubated at 30 °C for 24-48 hours. Identification of yeast species was performed by Vitek® 2 system (bioMérieux, France) using Vitek® 2 YST ID diagnostic cards for yeast.

Detection of anti-gliadin levels

Serum was collected from all study subjects at the same time as the swabs. Two types of antibodies against AGA were determined in the serum, including IgA and IgG by ELISA assay [10]. Levels of IgA and IgG anti-gliadin antibodies were determined using highly purified alpha-gliadin kit (AESKU. Diagnostics. Wendelsheim, Germany). The serum sample was diluted 1:101 and incubated in the ELISA microplate coated with the specific antigen. AGA levels in manufacture's manuals are: < 12 U/ml is normal, 12-18 U/ml is moderate, and > 18 U/ml is positive.

Ethical approval

The study was carried out in accordance with the Declaration of Helsinki and was endorsed by the local ethics committee of the authors College, No. 200 in June 2020. Informed written consent was obtained from all subjects before they were admitted to the study.

Statistical analysis

Data were analysed statistically with one-way analysis of variance (ANOVA) using Microsoft Excel application in Microsoft Windows 7. The level of $p < 0.05$ was considered as significant.

RESULTS

Levels of two types of AGA were evaluated in all subjects in this case-control study. All patient and control groups were negative for the IgG AGA. Antibodies against AGA IgA were determined at a concentration > 18 U/ml (positive) in only four patients (8%), with a significant difference from the control ($p = 0.003$), but not with other VVC patients ($p = 2.01$). Meanwhile, 7 patients (14%) showed moderate concentration (12-18 U/ml) of these antibodies. IgA AGA showed good specificity (84.76%) in VVC patients with 90% specificity. There was no relationship between the concentration of IgG and IgA where they were clustered on

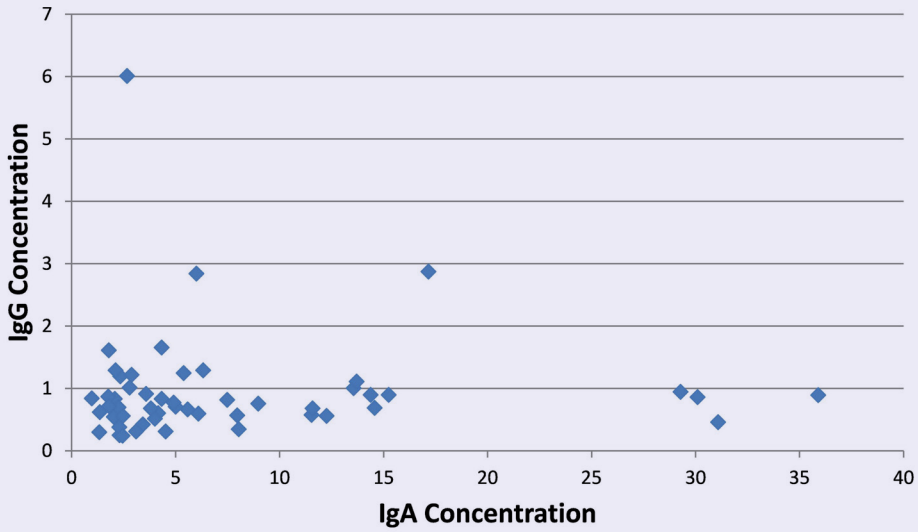

Figure 1. *Concentration of IgA AGA and IgG AGA in VVC patients.*

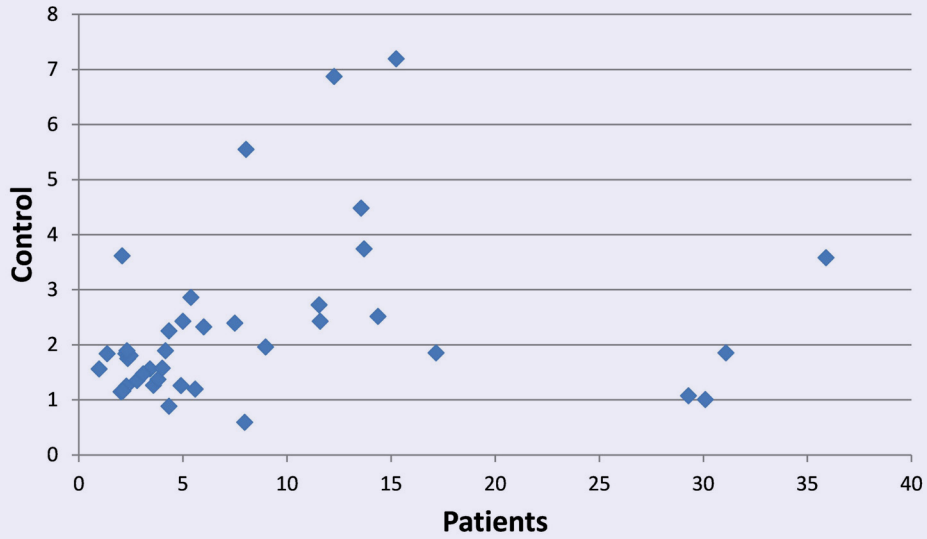

Figure 2. *Concentration of IgA AGA in VVC patients and control group.*

1-5 U/ml (**Figure 1**). There was an inconsistent positive relationship between patients and the control group in the concentration of IgA AGA. Levels of IgA AGA are higher in patients than in the control group. The IgA AGA cutoff value was set to 1-5 U/ml (**Figure 2**, **Table 1**).

Of the four patients with VVC who showed a positive result with IgA AGA, two patients were in the 24-32 age group (4%), with one patient in age group 15-23 years and another in group 33-41 years. The positive moderate results of the IgA AGA were 7 patients mostly in the 24-32 age group (10%) with a significant difference from other patients, while another one each were observed in age group 15-23 years and 42- 50 years (**Table 1**).

DISCUSSION

Vulvovaginal candidiasis (VVC) is a common genital disease which affects millions of women each year [1]. About three-quarters of all women are infected with VVC during their reproductive years [10]. A high prevalence of VVC may cost millions of dollars due to prescription drugs and physician visits [2]. The VVC can be symptomatic or asymptomatic. Several *Candida* species can cause VVC [1]. It is estimated that 75% of all women may have VVC during their lifetime and that 90% of them are infected with *C. albicans* [11].

The results of this study indicated that there were no positive IgG AGA levels in patients with VVC.

Table 1. *Anti-gliadin levels in patients with vulvovaginal candidiasis in correlation with age.*

Subject groups	Age group (year)	No. of patients (%)				Total n (%)
		AGA IgG	Anti-gliadin IgA level (U/ml)			
			Positive (> 18)	Equivocal (12 – 18)	Negative (< 12)	
Patient (n = 50)	15-23	0	1 (2)	1 (2)	16* (17.7)	18 (20)
	24-32	0	2 (4)	5* (10)	13* (14.4)	20 (22.2)
	33-41	0	1 (2)	0	5 (5.5)	6 (6.6)
	42-50	0	0	1 (2)	5 (5.5)	6 (6.6)
Control (n = 40)	20-30	0	0	0	40 (44.4)	40 (44.4)
Total n (%)		**0**	**4 (4.4)**	**7 (7.7)**	**79 (87.7)**	**90**

*Significant differences between anti-gliadin levels in the same age group.

Meanwhile, four patients had higher levels of positive AGA IgA. Detection of AGA with its two classes was the first test used for diagnosis of CD since 1950 and now has becomes a less significant test [3, 4]. The potential for candidiasis to induce AGA production was proposed based on the detection of positive AGA results in two patients with chronic mucocutaneous candidiasis [8, 9]. The first case detected a slightly elevated level of AGA in a boy with chronic mucocutaneous candidiasis that decreased later [8]. In the second case of chronic mucocutaneous candidiasis, the levels of IgG AGA were higher (365 U/L), but there was no increase in the AGA IgA level [9].

AGA IgA was detected in some patients with VVC in the current study with levels that are typically found in CD patients. IgA AGA is the most important type of AGA for diagnosis of CD [12]. The promotion of AGA by *Candida* spp. is mainly dependent upon the presence of the Hwp1 protein in its cell wall [7]. Hwp1 is a specific protein of *C. albicans* hyphae which may be used as a substrate for the enzyme human transglutaminase (TG) [7, 10]. The binding of human TG with Hwp1 produces a complex that leads to production of anti-tTG antibodies and AGA [6, 7]. Thus, the AGA level in candidiasis patients may be elevated under the activity of the Hwp1 protein of *C. albicans*. This proposed mechanism has been demonstrated by identifying higher levels of specific antibodies to anti-Hwp1, AGA and anti-tTG in the presence of *Candida* spp. in patients with CD than in healthy people [5]. The above description of the ability of the Hwp1 protein in *Candida* spp. to stimulate AGA production can explain the elevated levels of IgA AGA in some patients with VVC of the present study.

Based on the results of this study, positive IgA AGA was observed primarily in two VVC patients aged 24-32 years and one each in the 15-23 and 33-41 age groups. These findings indicate that positive IgA AGA is common in young patients with VVC, which differentiates it from CD patients. Levels of IgA AGA are often positive in children with CD more than in youth [12, 13]. Positive IgA AGA results in Pakistani CD patients were higher among youth and gradually declined with age [13]. Several studies have indicated that the level of IgA AGA is most often increased in children. Measurement of IgA AGA in 150 Iraqi children with CD revealed that younger children (1 to 5 years old) with high levels of IgA were most common compared to other ages [12].

Since AGA is specifically induced by *Candida* infections and not by other organisms, the other significant findings of the current study are to determine the type of treatment used for vulvovaginal infection. Clinical features of many vulvovaginal infections caused by various pathogenic microorganisms such as bacteria or parasites usually difficult to differentiate from that caused by fungal infection (VVC) [1, 2]. Thus, the treatment of VVC depends mainly on the identification of the causal agent and not only on clinical characteristics. In addition, significant elevated levels of AGA IgA make this type of antibody useful for both VVC diagnosis and clinically important to differentiate fungal infection from bacterial or parasite infection.

Study limitations

Many limitations are present in the current study. The smallest number of patients is the most critical one. The period of this study saw many women with suspected VVC seek treatment from gynaecological consultants at AL-Zahraa hospitals in the AL-Najaf province of Iraq. *Candida* infection in the vagina was confirmed by clinical and laboratory

tests in only 50 women. Several patients who were excluded were diagnosed with bacterial infections or trauma injuries. The selected women were required to have no suspected underlying factors for AGA, which was the second limitation of the number of participating patients in this study. Those who suffered from autoimmune diseases or other effectively diseases at the AGA level were also excluded. The AGA is a highly sensitive indicator that can be triggered by multiple disorders in the human body.

CONCLUSIONS

This primary study's findings can inspire further research into the relationship between VVC and AGA levels. It is premature to determine a strong correlation between these factors based on the current results. The final decision regarding such a type of correlation requires further studies on a large number of certified patients with VVC. Many prospective markers can be added to the diagnosis of VVC in case of confirming a strong relationship between infections with VVC and an increase or decrease in levels of AGA. The first is that AGA measurement can be useful in differentiating between VVC caused by fungi from those with the same clinical characteristics caused by bacteria or parasites [1, 12]. Thus, determining the correct causative agent will make VVC treatment more meaningful within a short time. The second is confirmed that AGA is not specific to one disease such as CD [3, 4]. The third conclusion can support the ability of *Candida* spp. to stimulate AGA production by its excretions or structural components such as the Hwp1 protein [6]. The fourth conclusion is that the measurement of AGA, especially of the IgA class, mainly provides an indicator of the potential value of this antibody for the diagnosis of VVC in some cases.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

A.A.A.: Conceptualization, formal analysis, investigation, writing - original draft, supervision. M.J.M.: Methodology, project administration. A.A.A., M.J.M.: Resources. M.J.M. Software.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethical approval (IRB) was obtained from the ethical committee of the College of Medicine, University of Karbala with a No. 200 in June 2020.

Informed consent

All participants were volunteers and signed a consent form.

Data sharing

Data are available under reasonable request to the corresponding author.

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