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Humoral immune response to COVID-19 infection or vaccination among celiac disease patients

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Abstract

Introduction: *Celiac disease (CD) is the most common autoimmune disease (AD) of the small intestine, affecting 1-2% of the population globally. It is characterized by the serological presence of autoantibodies (Abs), tissue transglutaminase antibody (tTGA), immunoglobulin (Ig) A, and IgG. Production of antibodies against SARS-CoV-2 after infection with the virus or vaccination is not well understood, especially among CD patients. The goal of this study was to measure the IgG antibodies in Jordanian patients infected with or vaccinated against the SARS-CoV-2 virus with different types of vaccines (Pfizer-BioNTech BNT162b2, Sinopharm BBIBP-CorV or Oxford-AstraZeneca ChAdOx1-S) and compare them with the levels in non-celiac controls. IgG levels induced by different vaccines were also compared.*

Material and methods: *The data for this cross-sectional study were obtained via a survey, whereby respondents were identified through convenience sampling. The healthy controls were given Questionnaire A while CD patients completed Questionnaire B. The blood samples from all participants were tested for the COVID-19 nucleocapsid protein (NP) IgG serum levels for participants previously infected with SARS-CoV-2, and spike (S) protein (S1/S2) IgG serum levels for vaccine recipients.*

Results: *The study involved 116 individuals, 60 (51.7%) of whom were CD patients. The NP IgG serum levels in the infected and S1/S2 IgG levels in the vaccinated CD patients were significantly lower than the levels in controls (48.3 ±44.5 vs. 81.1 ±34.4 and 49 ±45.8 vs. 75.7 ±38.6, p = 0.002). Moreover, only the Pfizer vaccine induced significantly more IgG antibodies in controls compared to CD patients (88.8 ±29.1 vs. 58.3 ±45.4, p = 0.01). On the other hand, the IgG levels were significantly higher in CD patients who received the Pfizer relative to the AstraZeneca vaccine (58.3 ±45.5 vs. 13.0 ±23.6, p = 0.03). After adjusting for presence of CD, age, sex, body mass index (BMI), comorbidities, vaccine type, smoking, gluten adherence, and time since infection or vaccination, SARS-CoV-2 S1/S2 IgG Abs and/or NP IgG Abs positivity was significantly associated with CD absence and negatively with vaccine type (AstraZeneca) with the odds ratios (ORs) of 9.6 (95% CI = 1.5-59.2, p = 0.015) and 0.03 (95% CI = 0.004-0.244. p = 0.001), respectively.*

Conclusions: *We concluded that patients with CD had lower SARS-CoV-2 S1/S2 IgG Abs and NP IgG Abs levels than controls, and CD patients who received the Pfizer vaccine had higher IgG levels than patients who received the AstraZeneca vaccine. We recommend that further research be conducted to address the dynamics of the antibody responses in CD patients regarding COVID-19 infection.*

Key words: *celiac disease, autoimmune, COVID-19, vaccination, IgG antibody.*

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Introduction

COVID-19 is caused by severe acute respiratory syndrome-like coronavirus 2 [1], which has so far claimed over 4.26 million lives and has caused 238 million infections worldwide [2]. In Jordan, the recorded cases have reached more than 1.5 million, with over 12,372 deaths [3].

To date, treatments for COVID-19 have mainly focused on alleviating the symptoms and offering supportive therapy. However, one of the most effective strategies for mitigating the COVID-19 pandemic is global vaccination [4]. As of 28 December 2021, 8,806,100,479 doses of COVID-19 vaccines had been given worldwide, while

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8,220,492 doses of Pfizer-BioNTech BNT162b2, Sinopharm BBIBP-CorV or Oxford-AstraZeneca ChAdOx1-S had been administered in Jordan [3].

Available evidence also indicates that COVID-19 infection can have an asymptomatic course, or can present with fever, malaise, and dry cough in the initial phase, during the invasion and infection of the upper respiratory tract [5]. Patients may also experience gastrointestinal (GI) symptoms such as abdominal pain, vomiting and diarrhea, and signs of systemic involvement.

The GI involvement in COVID-19 may be due to the capacity of SARS-CoV-2 to directly infect the intestinal tract, as the angiotensin-converting enzyme 2 spike can easily penetrate host cells [6]. Furthermore, as ACE2 is present on the esophageal epithelium, in the small bowel enterocytes from the ileum, and in the colon's colonocytes [7], the proximity between the luminally residing SARS-CoV-2 virus and its specific receptor creates the optimal conditions to infect, penetrate, replicate and damage the host cells and finally be excreted and transmitted via passed stools [8].

Celiac disease (CD) is the most common autoimmune disease (AD) of the small intestine, estimated to affect 1-2% of the world population [9]. It is a classic example of a multifactorial disease involving genetic and environmental factors, whereby the specific allotype HLA-DQ2 molecule is found in about 90-95% of CD patients [10, 11].

Furthermore, serological presence of certain autoantibodies, including immunoglobulin (Ig)A anti-tissue transglutaminase antibody (tTGA), is indicative of CD. Except for CD patients with IgA deficiency, in whom IgG antibodies against deamidated gliadin (IgG-anti-dGli) or IgG-anti-tTG or IgG anti-endomysium antibodies (EMA) can be used although they have lower specificity and sensitivity and they are less satisfactory for dietary adherence monitoring [12, 13], the serologic tests need to be confirmed by duodenal mucosal biopsies showing duodenal villous atrophy, increased intraepithelial lymphocyte (IEL) levels, and crypt hyperplasia depending on the Marsh-Oberhuber classification (they are all Marsh 3a or greater). CD patients are advised to follow a gluten-free diet (GFD), which generally leads to good symptom control, complete recovery of duodenal stricture that is demonstrated by re-biopsy, and a good prognosis.

The authors of a previous study conducted in Jordan reported an incidence of CD of 1 in 2,800 live births, with an estimated point prevalence of 7 : 100,000 [14]. The serological prevalence of CD in Jordanian school children was estimated at 1 : 124, corresponding to 0.8%, with the 95% confidence interval (CI) = 0.5-1.3% [15].

It should be noted that the actual production of antibodies (Abs) against SARS-CoV-2 in patients with CD after vaccination is not well understood. In particular, in Jordan, the effect of COVID-19 infection and different vaccines on adults with CD requires further investigation. This gap in extant knowledge is addressed in the present study by measuring the IgG antibodies in CD patients infected with or vaccinated against the SARS-CoV-2 virus and comparing these findings with those obtained for non-celiac individuals. Moreover, the IgG levels after different types of SARS-CoV-2 vaccines are compared and their significance for the CD patients and non-celiac individuals is discussed.

Material and methods

This cross-sectional study was approved by the Ethics and Scientific Committees of the Faculty of Medicine at Mutah University, Jordan with reference number 31-2022. Informed consent was obtained from all participants, whose confidentiality was protected in line with the Declaration of Helsinki provisions.

The sample comprised 60 CD adult patients (mean age 38.7 ±11.788). They were diagnosed by serologic testing of celiac-specific IgA antibodies to human tissue transglutaminase. They had normal IGA levels, and it was confirmed by duodenal mucosal biopsies. The patients were a mixture of treated and active CD patients, and 56 non-celiac controls (mean age 43 ±13.074). They were previously screened for the presence of IgA antibodies to human tissue transglutaminase (tTG) in the gastro-intestinal clinic in Al-Karak Hospital as part of a screening study performed in the hospital and showed negative results and normal IgA levels. Both the patients and controls had a documented COVID-19 diagnosis and/or vaccination. All participants were recruited from different clinics at Al-Karak Hospital from September 2021 to November 2021.

Two questionnaires were designed to obtain pertinent information, whereby non-celiac controls completed Questionnaire A and CD patients were given Questionnaire B. All participants provided blood samples which were tested for the COVID-19 IgG serum levels.

Measurements and instruments

Questionnaire A and Questionnaire B included respectively 14 and 16 questions (both open and closed) in Arabic, as this is the official spoken language in Jordan. To ensure the instrument's validity, both questionnaires were assessed by a group of experts for question clarity and comprehension, as well as survey structure evaluation.

Both questionnaires inquired about respondents' age, sex, smoking, comorbid diseases, body mass index (BMI), date of COVID-19 infection or vaccination, type of vaccine taken, and any clinical signs and symptoms indicative of the coronavirus infection as well as related hospital admissions. Questionnaire B further included questions related to the age at CD diagnosis, adherence to a GFD, and GI symptom severity.

After obtaining serum samples, for patients with prior SARA-CoV-2 infection, Ichroma – which is a COVID-19 IgG antibody test against virus nucleocapsid protein (NP) with sensitivity and specificity of 95.8% and 97.0%, respectively – was used as a medical instrument for *in vitro* diagnosis [16]. A positive result was defined as an IgG level of 1.1 or more [17]. As the coronavirus spike (S) protein serves as the immunogen in all approved vaccines (except Sinopharm, which is based on the inactivated virus) [18], an antibody against S protein was used as a measure for humoral immunity elicited by these vaccines [19, 20]. For this purpose, LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay against a recombinant spike (S) protein (S1/S2) (DiaSorin S.p.A., Saluggia, Italy) was used according to the manufacturer's instructions. Results below 12.0 AU/ml were considered negative, 12.0-15.0 AU/ml borderline, and > 15 AU/ml positive. All measurements were carried out by trained laboratory employees from a local medical equipment business, who took all necessary biosafety precautions. SARS-CoV-2 IgG output is expressed in arbitrary units (AU/ml).

Statistical analysis

Frequencies and percentages were calculated to represent participant distribution across categories and means/medians were obtained for continuous variables, with standard deviations (SD) and ranges as measures of spread. Furthermore, between-group comparisons were carried out by a two-tailed *t*-test while one-way ANOVA followed by a post-hoc *t*-test was used for multiple comparisons. The data normality was ascertained by visually inspecting histograms and was confirmed by the Shapiro-Wilk test.

Moreover, logistic regression was performed to assess the impact of different factors (presence of CD, age, sex, BMI, comorbid diseases, gluten adherence, date of infection or vaccination, type of vaccine, and smoking) on the likelihood of reporting a positive SARS-CoV-2 S1/S2 IgG Abs and/or NP IgG Abs test. Another regression was conducted to determine how CD could predict adverse COVID-19 infection outcome and hospitalization. All tests were two-tailed, considering $p < 0.05$ statistically significant. All analyses were conducted using SPSS v16 and graphs were produced using RStudio.

Results

The study sample ($n = 116$) comprised 60 (51.7%) CD patients and 56 controls (48.3%), with the mean age of 39.5 (range = 18-64) and 43.5 (range = 18-76) years ($p = 0.068$), respectively. In both groups, at 42 (70%) and 41 (73.2%), females outnumbered males. Counts and percentages of participants regarding their gender, smoking status, history of hypertension, adherence to GFD, previously diagnosed COVID-19 infection, GI-associated symptoms, COVID-19-related hospitalization, as well as vaccination status, vaccine type, and antibody positivity were calculated. The means and standard deviations of BMI, time since CD diagnosis, COVID-19 virus infection, and vaccination in both CD patients and controls were determined and all findings are shown in Table 1.

Furthermore, an independent-samples *t*-test was conducted to compare the NP IgG serum levels in infected participants and S1/S2 IgG levels in vaccinated participants, and the results obtained for CD patients were compared with those related to controls. Analyses revealed that the IgG levels of infected as well as vaccinated individuals were significantly lower in the CD group compared to controls (48.3 ±44.5 vs. 81.1 ±34.4 and 49 ±45.8 vs. 75.7 ±38.6, $p = 0.002$). The ANOVA test conducted on the full sample further revealed that IgG levels were significantly higher after Pfizer vaccination relative to Sinopharm and AstraZeneca vaccines (69.2 ±42.6 vs. 54.0 ±44.8 vs. 38 ±44.1, $p = 0.04$), as shown in Table 2.

Although a larger proportion of CD patients was unvaccinated compared to controls (11.7% vs. 7.1%), this difference is not significant, as shown in Table 1, so that bias will not impact the results. To differentiate between CD patients and controls in terms of their response to different vaccines, the mean COVID-19 S1/S2 IgG antibody levels of the CD group and non-celiac controls were compared and the findings are presented in Figure 1. The analyses showed that the antibody levels produced in the control group were higher than in CD patients, but only the difference related to the Pfizer vaccine was statistically significant (88.8 ±29.1 vs. 58.3 ±45.4, $p = 0.01$).

Based on the results yielded by one-way ANOVA followed by the post-hoc *t*-test, and according to COVID-19 S1/S2 IgG values, the IgG levels in CD patients were also significantly higher in those who received Pfizer than those who received AstraZeneca vaccines (58.3 ±45.5 vs. 13.0 ±23.6, $p = 0.03$). However, no significant differences were found in the control group, as shown in Table 3.

Further analyses focusing on CD patients revealed that the most common CD-related GI symptom that increased in severity due to COVID-19 was stomach pain (46, 77%), while the most prevalent COVID-19-related symptom was fatigue (48, 80%), as shown in Figure 2.

In our study, an antibody titer was performed after 12 months (infection) and 5 months (vaccination), and seronegative results were noted in 10 (out of 60) CD patients and 2 (out of 56) controls. The logistic regression model was conducted, and after adjusting for the confounding factors related to SARS-CoV-2 S1/S2 IgG Abs and/or NP IgG Abs seropositivity, the results revealed that absence of CD was significantly positively associated with IgG positivity with an odds ratio (OR) of 9.6 (95% CI = 1.5-59.2, $p = 0.015$) and the vaccine type (AstraZeneca) was significantly negatively associated with IgG positivity with an odds ratio (OR) of less than 1 (95% CI = 0.004-0.244, $p = 0.001$), as shown in Table 4. However, after adjust-

Table 1. Characteristics of the study population

Parameter	Were you diagnosed with celiac disease?				*P*-value	95% CI
	Yes (*n* = 60)		No (*n* = 56)			
	n[a]	%[b]	*n*[a]	%[b]		
Gender						
Male	18	30	15	26.8	0.7	–0.20-0.13
Female	42	70	41	73.2		
Smoking status						
Smoker	10	16.7	11	19.6	0.68	–0.11-0.17
Non-smoker	50	83.3	45	80.4		
Previous COVID-19 infection						
Infected	36	60	33	58.9	0.91	–0.19-0.17
Uninfected	24	40	23	41.1		
Adherence to a GFD						
Strictly adherent to the GFD	36	60	0	0	–	–
Not strictly adherent to the GFD	24	40	56	100		
HTN						
Yes	35	58.3	19	33.9	0.008*	–0.42 to –0.06
No	25	41.7	37	66.1		
COVID-19 vaccination status						
Vaccinated	53	88.3	52	92.9	0.41	–0.06-0.15
Unvaccinated	7	11.7	4	7.1		
Hospitalization due to COVID-19						
Hospitalized	7	11.2	5	8.9	0.45	–0.16-0.07
Not Hospitalized	53	88.8	51	91.1		
Increase of CD related GI symptoms after COVID-19 infection						
Increased	51	85	–	–	–	–
Not affected	9	15	–	–		
SARS-CoV-2 S1/S2 IgG Abs and/or NP IgG Abs positivity						
Missing	3	5	8	14.3	0.03*	–0.26 to –0.01
Negative	10	16.7	2	3.6		
Positive	47	78.3	46	96.4		
Type of COVID-19 vaccine						
Pfizer	36	60	24	42.9	0.13	1.32-1.68
Sinopharm	17	28.3	25	44.6		
AstraZeneca	7	11.7	7	12.5		
Variable	**Mean[c]**	**SD[d]**	**Mean[c]**	**SD[d]**	***P*-value**	**95% CI**
BMI	25.1	6.8	29.5	5.5	0.00*	–6.64 to –2.03
Time since COVID-19 infection (months)	12.1	4.6	13.9	5.4	0.16	–4.20-0.73
Time since COVID-19 vaccination (months)	5.3	2.1	5.1	1.4	0.46	–0.46-0.99
Time since CD diagnosis (months)	118.8	81.01	–	–	–	–

**p < 0.05, n – count, SD – standard deviation, GFD – gluten-free diet, HTN – hypertension, CD – celiac disease, GI symptoms – gastrointestinal symptoms, Abs – antibodies, BMI – body mass index [a]Data expressed as counts, [b]data expressed as percentages, [c]data expressed as means, [d]data expressed as SDs*

Table 2. Mean COVID-19 immunoglobulin G (IgG) serum levels according to presence of celiac disease (CD) and vaccine types

Variables	Mean ±SD	*P*-value	95% CI
SARS-CoV-2 NP IgG antibodies			
CD	48.3 ±44.5	0.002*	–53.5 to –12.0
Control	81.1 ±34.4		
SARS-CoV-2 S1/S2 IgG antibodies			
CD	49 ±45.8	0.002*	–44.1 to –9.2
Control	75.7 ±38.6		
S1/S2 IgG antibodies after different types of COVID-19 vaccines			
Pfizer	69.2 ±42.6	0.04*	4.7-56.7
Sinopharm	54.0 ±44.8		
AstraZeneca	38 ±44.1		

**p < 0.05, 95% CI – 95% confidence interval, SD – standard deviation, CD – celiac disease. Dependent variable: COVID-19 IgG*

ing for different associated factors, CD did not emerge as a risk factor for hospital admission due to COVID-19 complications.

Discussion

This study aimed to measure the NP and S1/S2 IgG antibodies in CD patients who were infected or had been vaccinated against COVID-19, respectively, and compare the findings with the results obtained for non-celiac controls. Its further objective was to compare the IgG levels after different types of vaccines, as such investigations have not been conducted in Jordan.

Our results indicate that the COVID-19 IgG serum levels were lower among CD patients, concurring with the findings reported by Opri *et al*. [21], who found that patients with CD had a statistically significantly lower rate of protective antibody titer than controls after receiving a hepatitis B vaccine. Zingone [22] similarly found that the prevalence of seroprotective levels of anti-HBVs detected eleven years after primary immunization, as well as the frequency of response to a booster dose of vaccine, was lower in CD patients compared to the non-celiac controls.

Celiac disease is associated with primary immunodeficiency. It occurs in approximately 8% of patients with isolated IgA deficiency [23], and it is also relatively common in many other immunodeficiency diseases [24]. Although the CD patients in our study were positive for IgA antibodies to human tissue transglutaminase (tTG), the determination of other immunological parameters in patients with CD is not standard and needed to be tested more as it may affect both the response to the vaccine and for the infection that was shown in our study.

The HLA system is a critical host genetic factor that plays a vital role in determining the outcome of many infectious diseases, including HIV and severe acute respiratory syndrome (SARS) [25]. Associations between HLAs and the development and/or severity of SARS have been found in some populations [25, 26]. Further, Zimmermann and Curtis suggested that HLA-DQ2 or HLA-DQ8, which confer a genetic predisposition to CD, may be the drivers of lower responses to vaccination in CD patients [27].

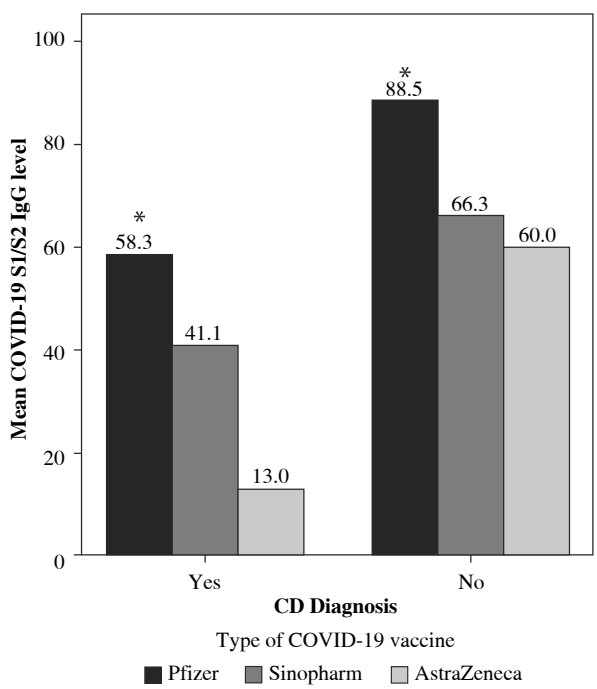

Fig. 1. Mean COVID-19 IgG antibody levels after different vaccine types in the CD patients and non-celiac controls; **p* < 0.05

Moreover, Lerner [28] stated that, while CD does not increase the likelihood of COVID-19 infection, parts of the CD population might be at high risk [29]. Zhen *et al*.

Table 3. Mean difference in immunoglobulin G (IgG) levels as well as the *p*-value and confidence interval for the ANOVA test and the post hoc test between the three vaccine types

	CD group			Non-celiac controls		
	MD	***P*-value**	**95% CI**	**MD**	***P*-value**	**95% CI**
Pfizer						
Sinopharm	17.2	0.3	–11.6- 46.0	22.2	0.57	–2.14-46.5
AstraZeneca	45.3	0.04*	2.2-88.4	28.5	0.08	–9.47-66.4
Sinopharm						
Pfizer	–17.2	0.23	–46.0-11.6	–22.2	0.57	–46.51-2.14
AstraZeneca	28.1	0.23	–18.4-74.7	6.3	0.72	–31.85-44.4
AstraZeneca						
Pfizer	–45.3	0.04*	–88.4 to –2.2	–28.5	0.08	–66.47-9.47
Sinopharm	–28.1	0.23	–74.7-18.4	–6.3	0.72	–44.48-31.8

**p < 0.05, 95% CI – 95% confidence interval, MD – mean difference. Dependent variable: COVID-19 IgG*

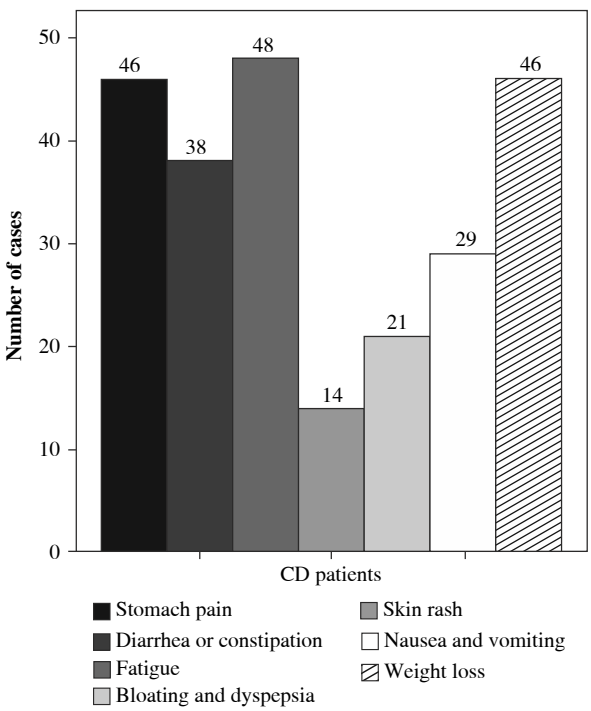

Fig. 2. Prevalence of symptoms in CD patients

Table 4. The likelihood of positive SARS-CoV-2 S1/S2 immunoglobulin G (IgG) Abs and/or NP IgG Abs tests in the study population

Variable	**Likelihood of positive COVID-19 test**	
	Adjusted OR (95% CI)	***P*-value**
No CD	9.6 (1.5-59.2)	0.015*
Vaccine type (AstraZeneca)	0.03 (0.004-0.244)	0.001*

**p < 0.05, OR – odds ratio, 95% CI – 95% confidence interval, CD – celiac disease*

[30] similarly found that patients with CD had a similar likelihood of contracting the virus when compared with the non-celiac group [31]. In contrast, our results indicate that CD is a statistically significant predictor of having COVID-19 IgG seronegative results and a higher risk of COVID-19 infection.

The seronegativity in CD patients could be due to the presence of the HLA-DQ2.5 heterodimer, which is an HLA class II molecule that is found in about 90% of CD patients. It has been shown that HLA-DQ2.5 has a reduced ability to interact with T helper cells, which could decrease CD patients' antiviral response [32, 33], making them more susceptible to COVID-19 infection.

Furthermore, we found no significant association between having CD and the need for hospitalization due to COVID-19 infection complications. A similar conclusion was reached by Uche-Anya *et al*. [34] as well as Faye *et al*. [34, 35], who noted that the risk of hospitalization due to the infection was not significantly increased in patients with CD or AD. We did however find a significant difference between CD patients who were vaccinated with Pfizer and AstraZeneca in terms of IgG serum levels, aligning with the results reported by Lim *et al*. [36].

This study has some limitations, including the small sample size and the convenience sampling method, which may lead to selection bias. Moreover, the median age of all the participants was 41.5 years, and about 71.6% were female. Therefore, the results reported here might not be generalizable to other populations. Also, females are less frequent in CD vs controls, which may suggest a population bias. Furthermore, a large proportion of patients (40%) are "not committed" to a GFD, which would indicate that this proportion of patients have active celiac disease, and this will likely impact the results. Thus, long-term studies with larger and more heterogeneous samples are needed to examine the dynamics of the antibody responses in CD patients regarding the COVID-19 infection as well as

the different COVID-19 vaccines. Longer-term studies are needed to determine whether CD patients have a different immune response to COVID-19 vaccines compared to the general population.

Conclusions

The results yielded by this study indicate that patients with CD had lower IgG levels than controls, and CD patients who received the Pfizer vaccine had higher IgG levels than patients who received the AstraZeneca vaccine. The factors associated with seropositive IgG levels were absence of CD, which showed a positive association, and vaccine type (mainly AstraZeneca), which showed a negative association. Moreover, CD patients who took part in our study were not identified as being at increased risk of hospitalization from COVID-19 but were at a greater risk of getting infected. Thus, they should follow the public health advice aimed at the general population, and should receive COVID-19 vaccination (two doses and a booster dose) as soon as possible. Finally, we recommend that further research be conducted to address the dynamics of the antibody responses in CD patients regarding COVID-19 infection, as well as the different COVID-19 vaccines for a longer term, to determine whether celiac disease truly represents a concern for increased COVID-19 risk.

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The authors declare no conflict of interest.

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