Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: Jostein H. Ibsen, Adity Chopra, Eline Benno Vaage, John T. Vaage, Fridtjof Lund-Johansen & Knut E. A. Lundin (2022): Immune responses to SARS-CoV-2 vaccines in celiac disease, Scandinavian Journal of Gastroenterology, DOI: 10.1080/00365521.2022.2114809

To link to this article: https://doi.org/10.1080/00365521.2022.2114809

Published online: 01 Sep 2022.

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
https://doi.org/10.1080/00365521.2022.2114809

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ORIGINAL ARTICLE

Immune responses to SARS-CoV-2 vaccines in celiac disease

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ABSTRACT

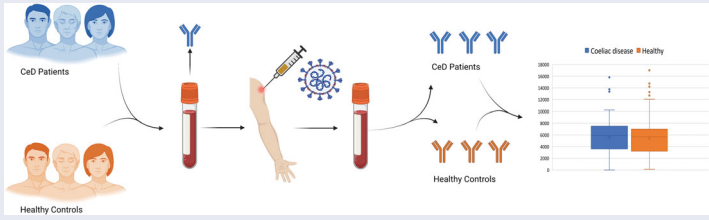
Background and aims: SARS-CoV-2 infection and development of the disease COVID-19 is a serious threat to our society. Effective vaccines have now entered the market, but most patient populations were not included in the registration clinical trials. There is evidence that patients with celiac disease (CeD) have reduced effect of vaccines such as the hepatitis B vaccine. Hence, we investigated the humoral response to SARS-CoV-2 vaccines (Chadox1, Comirnaty and Spikevax) in CeD patients and healthy controls.

Methods: CeD patients from a patient registry at Oslo University Hospital were invited to donate serum samples before and after vaccination. We sent out 1537 invitations and received paired samples from 85 individuals. These were compared with similar samples from 238 healthy controls. Sera were analyzed for antibodies to the Spike protein from SARS-CoV2 and the receptor-binding domain. The results where then converted into binding antibody units (BAU)/ml to compare.

Results: Prevaccination samples showed that very few patients had been earlier exposed to Sars-CoV2 and the antibody levels were low. Postvaccination analysis showed overlap of antibody levels between CeD and healthy controls. On average, the CeD patient group had 5555.0 BAU/ml (330.1 SD) while the average in healthy controls was 5419 (184.7 SD).

Conclusion: The humoral response to SARS-CoV-2 vaccines in CeD patients is similar to that observed in healthy controls.

GRAPHICAL ABSTRACT



(Created with BioRender.com)

Abbreviations: Ab: antibody; AVG: average; BAU: binding antibody units; CeD: celiac disease; CI: confidence interval; HBV: Hepatitis B Virus; HLA: human leukocyte antigen; OUH: Oslo University Hospital; RBD: receptor -binding domain; SD: standard deviation

ARTICLE HISTORY
Received 6 May 2022
Revised 9 August 2022
Accepted 15 August 2022

KEYWORDS
Celiac disease; SARS-CoV-2; COVID-19; vaccine response; immunology; immune disease

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and following development of the disease COVID-19 is a serious threat to public health and safety [1]. The estimated number of cases in Norway per 10 April 2022 was 1.4 million [2]. In addition, the COVID-19 pandemic and the quarantine measures put in place to curb the spread of the virus have put a significant strain on public health [3]. Multiple vaccines were over the course of 2020 made ready to enter the market after very rapid testing and approval procedures [4,5]. These vaccines are globally in widespread use. The vaccines are strongly protective against severe COVID-19, but certain patient populations are still at risk [6,7]. In Norway per January 2022, 90.7% of the adult populations have received their second dose and large parts have also received a third dose [8].

Many patient groups were not included in the vaccine registration trials. Later studies have shown attenuated responses in certain patient groups [9–19]. These groups included people with immune deficiencies and people taking certain immunosuppressing medications such as anti-TNFα

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and anti-CD20 antibodies [20,21]. Identification of these patient groups is important for the implementation of tailored vaccination regimens

Celiac disease (CeD) is an immune disease of the small intestine with general and local manifestation [22]. Approximately 1%–2% of the population is affected by CeD [23]. The abnormal immune response in CeD is closely linked with the human leukocyte antigen (HLA) genotypes HLA-DQ2 and HLA-DQ8 [22]. Nonresponsiveness to Hepatitis B virus (HBV) vaccination has shown a connection to certain HLA genotypes that have strong relationships with CeD. It has also been noted that CeD patients have a lower probability of responding to HBV vaccination [24,25].

Zhen et al. [26] did not find evidence that CeD is associated with a higher risk for severe outcome of COVID-19, but the sample size was limited. It seems possible that CeD patients have attenuated effects of SARS-CoV-2 vaccination, and this would warrant earlier booster vaccination. The aim of the present study was to determine if the humoral response to SARS-CoV-2 vaccines (Chadox1, Comirnaty and Spikevax) in CeD patients is different from that observed in healthy controls.

Methods

Between January 2021 and September 2021, 1537 CeD patients identified from the registry at Oslo University Hospital (OUH) were invited to participate. A single letter with instructions to have prevaccine and postvaccine serum samples taken with their general practitioner were sent without any follow-up. Possible costs for the participants were not covered. Eligible patients were over the age of 18 years and diagnosed with CeD by intestinal biopsy [27]. In addition, prevaccine and postvaccine samples from 238 individuals from the OUH biobank were included in the study as a healthy control group. The invitation letter contained an informed consent form that was signed physically or digitally by the participants.

The consenting participants were instructed to take a blood sample before and after the vaccination. Participants could take the blood samples at their local physicians' office. The samples were sent directly to the lab at OUH to be analyzed. During blood sampling, it was noted if the patient were using any immunosuppressant medications that could affect the results. We have furthermore had access to the electronic patient charts, so details could be checked. The patients received the individual test results digitally (*via* HELSENORGE.NO)

OUH-COVID-19 general biobank is a collaborative effort containing control patients used in studies about COVID-19. A total of 254 patients from the biobank donated sera for the study as a healthy control group.

Measurement of antibodies

Semiquantitative measurement of antibodies to the receptor-binding domain (RBD) of the spike protein from SARS-CoV-2 wild-type (wt) was performed as described previously [28]. Briefly, bead-based arrays coupled with RBDs and spike proteins from ancestral/wild type SARS-CoV-2 (SARS-CoV-2wt) and variants of concern were incubated with serum diluted 1:100 for 1 h. For measurement of binding antibodies, the beads were labeled with R-phycoerythrin-conjugated antihuman IgG and analyzed by flow cytometry. Effects of sera on binding of ACE2 to RBDs from SARS-CoV-2 variants were measured as a proxy for neutralizing antibodies. Thus, beads were labeled successively with digoxigenin-conjugated recombinant ACE2 and antidigoxigenin and analyzed by flow cytometry. The median fluorescence intensity (MFI) of anti-Human IgG measured for beads coupled RBDs and spike proteins was divided by the MFI measured for beads with no virus protein (relative MFI, rMFI). We used a double cutoff for seroconversion: rMFI$>=$5 for beads coupled with RBDwt and rMFI$>=$5 for beads coupled with spike wt. The cutoff yields a sensitivity of 96% and a specificity of 99% [29]

Conversion to binding antibody units (BAU)/ml

Results obtained with a standard series prepared from a serum with 53,000 BAU/ml (Roche Elecsys anti-SARS-CoV-2 S assay) were used to convert rMFI to BAU/ml. Titers in the range of 1–500 were calculated on basis of rMFI measured for IgG binding to RBDwt. Higher titers were calculated on basis of results obtained with ACE2-RBD interactions. Thus, inhibitory effects of sera on ACE2-binding to RBDwt yield a dynamic range of 500–3000 BAU/ml, while inhibition of ACE2-binding to spike protein from the beta variant yield a dynamic range of 3000–20,000 BAU/ml. Signals measured with the standard series were used as input for regression in Excel to generate formulas for conversion of signals measured with test samples to BAU/ml.

Ethics

The study was conducted in accordance with the Helsinki Declaration. All participants gave informed consent to take part in the study. The study was approved by the Regional ethics committee, approval # 233704. All authors have reviewed and approved the final manuscript.

Results

As shown in Table 1, a total of 222 samples were collected from the CeD patients. 90 samples were from pre vaccination, 20 after first dose and 112 samples after the second dose of the vaccine. The prevaccination samples were used to investigate patients with past COVID-19 infection. The post vaccination samples collection date ranged from 3 to 178 days after vaccination. Only samples taken after 10 days and no later than 50 days were included in the final analysis. This was done to make it comparable to the healthy control samples. A total of 85 postvaccination samples from CeD patients were included; 238 healthy post vaccination samples were included with the sampling having a range of 10–50 days after vaccination.

The mean age in the patient group is 54 years with a range between 23 and 80 years and a SD of 14.7. In the control group the mean age is 45.3 with a range of 18–79 and a

Table 1. Summary of data of included patients postvaccination.

	Total ($n = 323$)	CeD group ($n = 85$)	Healthy controls ($n = 238$)	p value
Sex, *n* (%)				
Female		65 (0.77)	179 (0.75)	0.81
Male		20 (0.33)	59 (0.25)	
Age (y), mean (SD, range)		54 (14.7, 23–80)	45 (12.9, 20–68)	<0.001
Vaccine, *n*				
Combination with Chadox1		2	35	0.009
Combination of Comirnaty and Spikevax		7	14	
Comirnaty		54	149	
Spikevax		22	40	
Immunosuppressed, *n*		2	0	
Time after second Vaccination (days), mean (SD, range)		29.4 (10.3, 13–50)	20.1 (8.9, 10–50)	<0.001
Postvaccination, average (SD)				
RBD norm		204.2 (7.4)	223.1 (4.1)	<0.001
Spike FL norm		192.6 (6.7)	194.2 (3.0)	0.066
BAU AVG		5559.5 (331.0)	5419.2 (184.7)	0.63

SD: standard deviation; Chi square test is used for all variables except for age and 'time after 2. Vaccination' (independent sample *t*-test) and Prevaccination and Postvaccination samples (Mann Whitney U test two tailed).

SD of 12.8. The patient group included 65 (76.5%) females and 20 (23.5%) males while the control group had 179 (75.2%) females and 59 (25.8%) males. Among the CeD patient the serum was taken at average 29 (10.3 SD) days after the final dose of vaccination, while in the Control group the average was 21 (9.2 SD).

In the Control group, Comirnaty was the most common vaccine in use, since many of these individuals were hospital staff and therefore offered this vaccine; 104 Healthy controls took a double dose of Comirnaty. In the CeD group, there was a wider variety. In the CeD group, 54 took both doses of Comirnaty, 22 had Spikevax, while 7 had a combination of the two. Two patients also had a combination including Chadox1.

Prevaccination samples

As shown in Figure 1, in the patient group very few had been earlier exposed to Sars-CoV2 and the antibody levels were low. A total of three CeD patients had Antibody units 10 or above.

Postvaccination samples

Figures 2 and 3 and shows the post vaccination samples from the Healthy controls and the CeD patients as a result of RBD versus Spike FL. It shows a good response in almost all the patients. The CeD patients' BAU average (5559.5 mean (330.1 SD)) and the healthy controls BAU average (5419 mean (184.7 SD)) were statistically overlapping (two tailed p value of 0.63). The results (Figure 4) show that the humoral response to SARS-CoV-2 vaccines in CeD patients is similar to that observed in healthy controls. Figures 5 and 6 shows how the antibody levels compared to time after vaccination. Figures 7 and 8 compares the age of the patients to their response of the COVID vaccines. Both of these comparisons show complete overlap.

Subgroup analysis of patients from the two groups with the same type of vaccines yielded similar results. The two tailed p-value was 0.67 for the Comirnaty group, 0.15 for Spikevax and 0.75 for those with a combination. The two populations were also divided into different age categories: 20–29, 30–39, 40–49, 50–59 and 60–69. The analysis and p-values showed no significant difference within the age categories.

Nonresponders

Two CeD patients had a low vaccine response and can be spotted on Figures 3, 6 and 8. One of them uses immunosuppressant medicine with tacrolimus, prednisolone and mycophenolic acid due to kidney transplantation. The other suffers from common variable immunodeficiency, which may explain the absent vaccine response.

Discussion

We here report the serological responses to SARS-CoV-2 vaccinations of 85 CeD patients compares to a group of 238 healthy controls. Post vaccination analysis showed a complete between CeD patients and healthy controls. The results show that the humoral response to SARS-CoV-2 vaccines in CeD patients is similar to that observed in healthy controls. Thus, we could not observe any signs of possible immune deviation based on the HLA profiles (HLA-DQ2 and -DQ8) that are known to be associated with CeD [22].

The strength of this study is its concrete inclusion criteria. All the included patients had a definite, biopsy verified diagnosis of CeD before recruitment from the research biobank. Many of the patients included in this study donated sera both before and after vaccination. This makes it possible to study the development of the serologic response. Very few of the patients had a prevaccination sample suggesting earlier infection by SARS-COV-2.

Even though there are multiple strengths in this study, this kind of study also has its limitations. The time between vaccination and the blood sampling after the second dose were not standardized and varied between the patients. The use of immunosuppressant medication was noted on all participants. Other diseases were on the other hand not registered and could affect the results. However, a good immune response was observed in all patients except the one on immunosuppressant medication, which makes it unlikely for other diseases to affect the results. The study subjects were only followed until their second dose and not any further

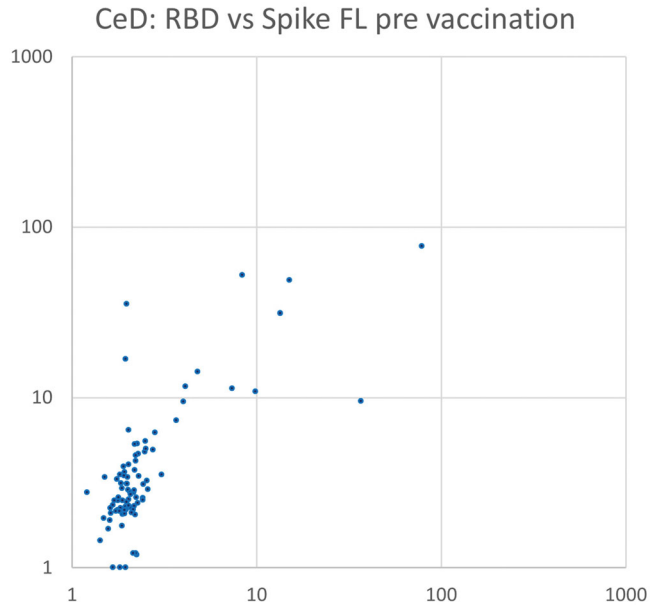

Figure 1. Prevaccination samples from CeD showing RBD versus Spike.

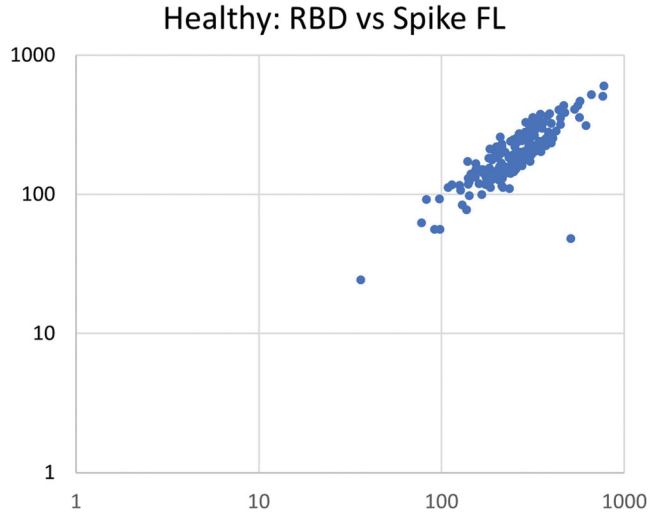

Figure 2. Postvaccination samples from Healthy showing RBD versus Spike FL.

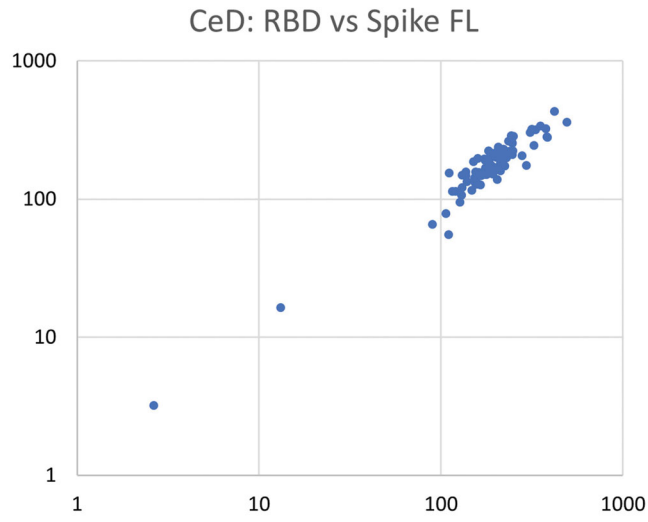

Figure 3. Postvaccination samples from CeD showing RBD versus Spike FL.

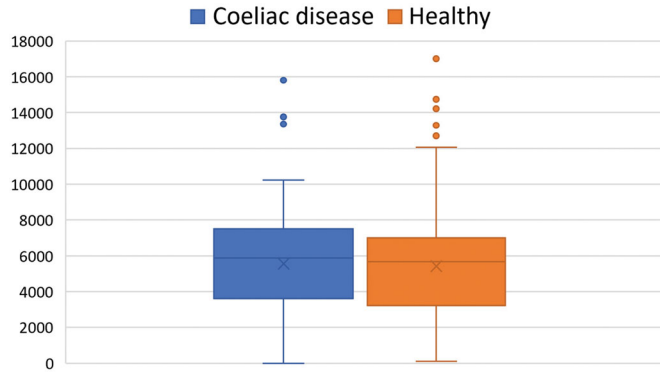

Figure 4. BAU AVG compared between Healthy controls and CeD patients.

after that, thus results of a third dose or even decline of antibody levels were not investigated.

In this study we also recruited patients vaccinated with Chadox1, Comirnaty and Spikevax. This might be a limitation of the study in that it adds additional factors that could impact the study results. Because of this we chose to perform additional analysis where we divided the two populations into smaller subgroups based on their type of vaccine. This yielded similar results as the main analysis.

The two populations were not homogeneous and contained a variety of different patients with both genders and a wide spread of ages from 23 to 80 years. Therefore, we also compared different age categories from the two populations with each other. All of these comparisons gave similar results to the main analysis.

This study is the first to explore SARS-CoV-2 vaccine responses in CeD. Elli *et al.* [30] investigated the antibody response in CeD patients that went through a Sars-CoV-2 infection and found no difference. Other studies have looked at the effectiveness of the vaccines in other immune diseases. Edelman-Klapper *et al.* [12] looked at the effectiveness of the vaccines in patients with IBD and found less response in those who were treated with immunosuppressants. Multiple other studies had similar findings with IBD and the typically immunosuppressant medication used treating the disease [9–13,16–19]. In recent times, multiple other studies have looked into immunosuppressant used as treatment for different diseases and found similar result in vaccine response [21,31,32].

This study was partly based on earlier findings about the link between certain HLA types connected to CeD and response to recombinant Hepatitis-B vaccination. Emel et al. [24] showed that the haplotype HLA-B8, DR3 and DQ2 which are linked to CeD increases that risk. However, these findings have not yet been found with any other vaccines than the hepatitis-B vaccine.

L Lorente et al. [33] found that certain HLA types had a higher risk of severe COVID-19, suggesting that different HLA profiles play a role in pathogenesis of SARS-CoV-2 infection. The study on the subject has still only been done on a small group and needs to be repeated with a larger pool of study participants before any firm conclusion can be drawn.

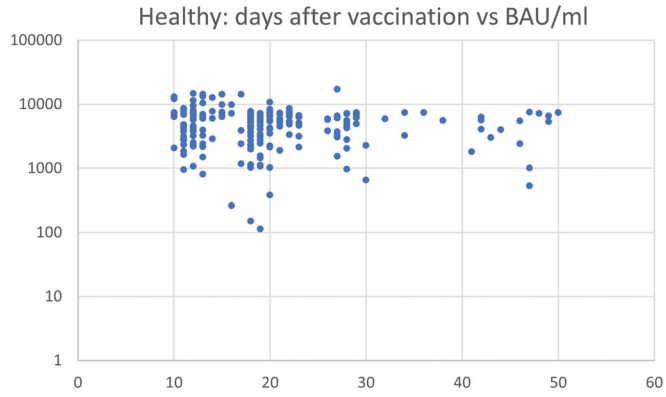

Figure 5. Healthy controls: days after vaccinations versus BAU/ml.

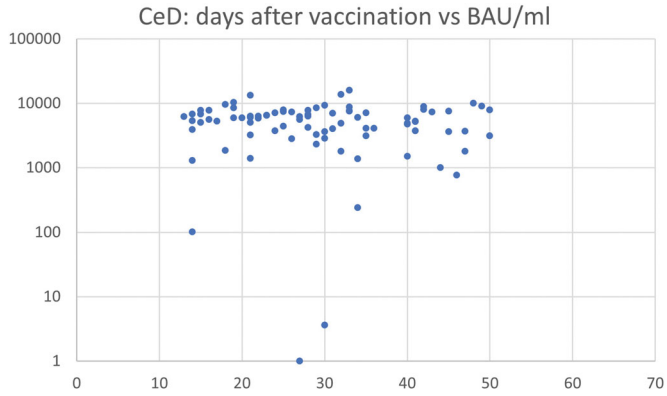

Figure 6. CeD patients: days after vaccinations versus BAU/ml.

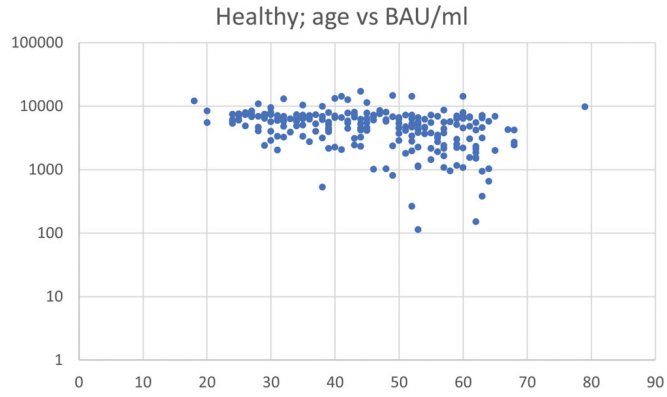

Figure 7. Healthy controls age versus BAU/ml.

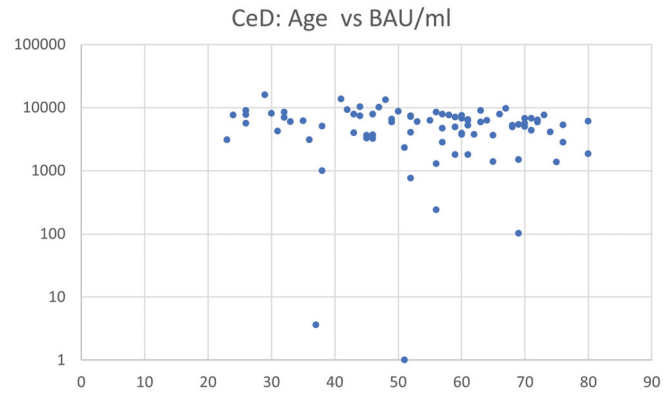

Figure 8. CeD patients: age versus BAU/ml.

Lebwohl *et al.* [34] research the risk of a higher risk of severe COVID-19 in CeD patients. The results concluded that there is no higher risk for CeD patients, which is in agreement with the findings in the present study.

HLA genotypes play an important role in the pathogenesis of CeD and possibly in the pathogenesis of COVID-19 [33,35]. However, when compared with the risk of severe COVID-19 in CeD patients and this study, it points toward other HLA types than the ones being associated to CeD. The results seem to point more toward that no responsiveness is connected to the use of immunosuppressant medications, than to HLA types.

Research about the effectiveness of vaccines on different patient populations is an important step against the COVID-19 pandemic. It is important to find out which patients have an increased risk and who may need unique vaccination plans. Based on the findings of this study, CeD patients can follow normal vaccine routines and expect the same protection as the rest of the population.

Acknowledgements

The authors thank our study participants for their efforts and time. The authors also thank OUS and all the personnel that have helped with collection and analysis of the blood samples. A special thanks also goes to the Siv Isaksen and Siv Kristianne Berg Furholm that have played an important part in recruiting participants. We also want to thank Stine Rosenqvist Lund for her efforts in this project.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by a grant from Stiftelsen Kristian Gerhard Jebsen [project SKGJ-MED-017].

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