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Research article

Adverse Events of COVID-19 Vaccines in Adolescents with Endocrinological Disorders: A Cross-Sectional Study

Short title: COVID-19 Vaccines in Endocrine Disorders

İbrahim Mert Erbaş[1], İrem Ceren Erbaş[2], Gözde Akın Kağızmanlı[1], Kübra Yüksek Acinikli[1], Özge Besci[1], Korcan Demir[1], Ece Böber[1], Nurşen Belet[2], Ayhan Abacı [1]
[1]Division of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey
[2]Division of Pediatric Infectious Diseases, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey

What is already known on this topic?
- Adverse events seen with COVID-19 vaccines in healthy adolescents are mostly similar to those in adults.
- There is a need for knowledge of the safety and adverse events of COVID-19 vaccines in special patient groups.

What this study adds?
- We showed that adverse event incidence and severity of COVID-19 vaccines in adolescents with endocrinological disorders were similar to healthy subjects.
- Autoimmune and non-autoimmune endocrine disorders had similar side effect profiles after COVID-19 vaccines.
- Treatment agents for endocrinological diseases did not cause a difference in the incidence of adverse events.

Abstract
Objective: We aimed to evaluate the adverse events seen after COVID-19 vaccines in pediatric patients with endocrinological problems and to compare them with healthy controls.
Methods: In this cross-sectional study, patients aged 12-18 years who applied to our department between January and May 2022 and were followed up for at least six months due to endocrine diseases, and healthy subjects in the same age group who had received a COVID-19 vaccine [BNT162b2 mRNA or inactivated vaccine] were included. Adverse events experienced after the vaccination were evaluated with a questionnaire.
Results: A total of 160 subjects (85 patients, 75 healthy controls) with a median age of 15.5 (25-75p: 14.1-16.9) years were included. The frequency of adverse events was higher in those vaccinated with the mRNA vaccine compared to the inactivated one in the first dose (p=0.015). The incidence of adverse events observed in the first and second doses of both COVID-19 vaccines was similar in the patient and control groups (p=0.879 and p=0.495, respectively), with local reactions as the most common one. The frequency of complaints was similar among the patients who received and did not receive any endocrinological treatment (p>0.05). The incidence and severity of systemic reactions were similar to healthy subjects in both vaccine doses, regardless of the underlying diagnosis, autoimmunity state, and the treatment regimen used in patients with endocrine diseases.
Conclusions: We found that adverse event incidence and severity of COVID-19 vaccines in adolescents with endocrinological disorders were similar to healthy subjects, in the early period post-vaccination.
Keywords: Coronavirus, vaccination, endocrine, pandemic, pediatrics

Ayhan Abacı, Division of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, 35330, İzmir, Turkey
+902324126076
ayhanabaci@gmail.com
0000-0002-1812-0321
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Introduction

Our world has been suffering from a pandemic for more than three years due to a disease called coronavirus disease-2019 (COVID-19), which was caused by the newly identified member of the coronavirus family named SARS-CoV-2 [1]. Since it has no effective treatment yet, the influence and spread of this disease continue. Therefore, vaccine studies have come to the fore and vaccines that are reported to be effective against the disease have begun to be used [2,3].

Although COVID-19 generally has a milder clinical course in the pediatric population, it is known to affect all age groups and serious complications such as multi-system inflammatory syndrome in children (MIS-C) have been observed in this age group [4,5]. Therefore, the necessity of initiating an effective vaccination program in children arose, and after studies focusing on this subject, the use of COVID-19 vaccines in children aged 12 years and older has been approved initially. Adverse events seen with these vaccines in adolescents are mostly similar to those in adults, though several serious events such as myocarditis were reported and raised concerns against these vaccines [6-8]. These results belong to healthy subjects, and the side effect profile of these vaccines in children and adolescents with chronic diseases is not yet clearly known.

Considering the systemic functions of hormones, questions were raised about the effects and side effects of vaccines against this disease in patients with endocrine disorders and several reports commented on this topic [9-12]. In addition, there were concerns that autoimmunity, which can be admitted as the cause of some endocrine diseases, may also change the response to COVID-19 and the vaccines. But similar recommendations like the normal population were made for those who did not receive conventional immunosuppressants, high-dose glucocorticoids, or immunomodulatory treatments such as biological agents for a systemic autoimmune disease [13]. However, these suggestions are mainly observed from adult studies and there is no data regarding the safety and adverse events of COVID-19 vaccines in children and adolescents with endocrine diseases or who were under treatment for these issues.

In this study, we aimed to investigate the adverse events observed after COVID-19 vaccines that were administered in our country [inactive SARS-CoV-2 and BNT162b2 messenger RNA (mRNA) COVID-19] in adolescents with endocrinological disorders and to compare these results with healthy subjects.

Subjects and Methods

This cross-sectional study was conducted in a single center between January and May 2022. Patients aged 12-18 years who applied to our Pediatric Endocrinology department and who had been followed up for at least six months due to an endocrinological disorder were included. Patients with any other underlying diseases, syndromes, or a history of drug use for non-endocrinological disorders were excluded from the study. Obesity was defined in patients with exogen obesity by a body mass index above the 95th percentile, and those with any underlying non-endocrinological causes of obesity were not included. The control group consisted of healthy adolescents in the same age group without any acute or chronic disease, that applied to outpatient clinics for routine check-ups. The main inclusion criterion for both groups was to be vaccinated against SARS-CoV-2. The medical history of the patients was confirmed by medical records and the vaccination status of all participants was verified by national registries. Individuals whose verification failed or whose medical records could not be reached were not included in the study.

All patients and healthy controls were vaccinated with at least one dose of COVID-19 vaccines. Information about the type of vaccine and the adverse events after vaccinations were recorded by a questionnaire, that was applied during the routine outpatient control. In our country, two types of vaccinations against SARS-CoV-2 (inactivated and BNT162b2 mRNA) became available for all children older than 12 years in September 2021. Individuals were free to choose their vaccine types and both vaccines were administered in two doses at a one-month interval.

Adverse events after vaccinations were evaluated by the Pediatric Infectious Disease department according to the recommendations made by the Vaccine Adverse Event Reporting System (VAERS) administered by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) [14]. Accordingly, redness, warmth, pain, or tenderness at the injection site was defined as a local reaction. Conditions causing permanent sequelae, life-threatening issues, or requiring hospitalization were classified as serious adverse events. Other remaining reactions (fever, rash, joint pain, etc.) were classified as non-serious systemic adverse events.

Statistical analysis

All statistical analyses were performed using the SPSS application for Windows version 24.0 (IBM Co., Armonk, NY, USA). The distribution of data was evaluated with the Kolmogorov-Smirnov test and the data were presented as number (%) for categorical variables, and median (25th-75th centile) for numerical variables. Comparisons were performed using the Pearson Chi-Square test and the Fisher Exact for categorical variables and using the Student's T-test or the Mann-Whitney U test for continuous variables, as appropriate. The McNemar test was used to compare the categorical data of two related groups. A p-value of <0.05 was considered statistically significant.

Ethics

The Local Ethics Committee of our institute approved the study (Ethics approval number: 2022/05-08), and we performed the study in accordance with the principles of the Declaration of Helsinki. An informed written consent form was provided by each subject and his/her parents before participating in the study.

Results

A total of 160 subjects (85 patients, 75 healthy controls) were included in the study, 56.3% of whom were girls. The median age of patients was 15.5 (14.1 – 16.9) years. Groups were similar in terms of age or gender (p=0.185 and p=0.563, respectively). Subjects were included after a median of 5 (5 – 6) months from the first dose of vaccination. Endocrinological diagnoses in the patient group were type 1 diabetes (41.1%, n=35), obesity (18.8%, n=16), hypothyroidism (17.6%, n=15), hypopituitarism (5.9%, n=5), polycystic ovarian syndrome (4.7%, n=4), autoimmune polyglandular syndrome type 2 (3.5%, n=3), hyperthyroidism (2.4%, n=2), pubertal disorders (2.4%, n=2), congenital adrenal hyperplasia (2.4%, n=2), and prolactinoma (1.2%, n=1). In total, 48 patients (56.5%) had an autoimmune disease. Sixty-three (74.1%) of the patients were under treatment for endocrine disorders. The most commonly used treatment agents were insulin (43.5%), levothyroxine (20%), and hydrocortisone (4.7%).

One hundred and fifty individuals (93.8%) were vaccinated with BNT162b2 mRNA [77 patients, 73 controls], and the remaining ones (6.2%, n=10) with the inactivated vaccine [eight patients, two controls] in the first dose. The frequency of adverse events was higher in those vaccinated with the mRNA vaccine compared to the inactivated vaccine (p=0.015), but it was similar among the patient and control groups regardless of vaccine type (p=0.879). Both groups experienced local events as the most common side effect of COVID-19 vaccines in the first dose (p=0.634). Regarding the systemic symptoms: fatigue, myalgia, and fever were the most common findings and the rate of all systemic events was not significantly different between the two groups (p=0.763) (Table 1). Sixteen subjects in each group (30.2% and 35.6%, respectively) suffered both local and systemic symptoms (p=0.692). A total of three individuals (one patient with hypothyroidism, one with obesity, and a healthy control) needed to admit the hospital, which was classified as a severe reaction, because of symptoms after the first dose. All of them had a complaint of fever and the one with obesity had also vomiting.

One hundred and forty-six individuals (77 patients, 69 healthy controls) completed the vaccination schedule with a second dose. The BNT162b2 mRNA vaccine was applied to 138 subjects [70 patients, 68 controls] and the inactivated vaccine was administered to eight [seven patients, one control]. Although we found a higher incidence of side effects in the second dose of the mRNA vaccine than in the inactivated one, this did not provide a significant difference (p=0.053). The frequency of adverse events was similar after the second dose of COVID-19 vaccines in both adolescents with endocrinological problems and healthy subjects (p=0.495). As seen with the first doses, the most common complaint was local reactions after the second dose (p=0.919). The rate of systemic events did not significantly differ between the two groups (p=0.958) (Table 2). Eighteen patients (36.7%) and 15 (33.3%) controls experienced both systemic and local reactions (p=0.813). One patient with obesity (because of myalgia and a severe local reaction) and two healthy adolescents (because of fever, myalgia, and vomiting) needed to admit the hospital after the second dose. There was no significant difference in the incidence of adverse events between the patient and control groups in each dose of each vaccine type (p>0.05) (Figure 1). The distribution of these events observed after each vaccination was given in Table 3.

When the patients were grouped according to the autoimmune origin of their diseases, the incidence of side effects did not differ among groups in each dose of the vaccine (p>0.05) (Table 4). Also, the frequency of adverse events was similar either in the first or second doses of COVID-19 vaccines between patients with and without treatment for the underlying endocrine diagnosis (p>0.05). When we compared the patients with and without autoimmune disorders that only received the mRNA vaccine (n=77), the incidence of adverse events was similar in both doses (p=0.896 and p=0.955 for the first and second doses, respectively). Also, the frequency of local and systemic reactions was similar between those two groups in both doses of the mRNA vaccine (p>0.05).

In children with endocrinological problems, 70.5% of those who experienced side effects at the first dose reported adverse events at the second dose (p=0.851). Eight patients with type 1 diabetes experienced hyperglycemia at the first dose, four experienced hyperglycemia at the second dose, and one patient had hypoglycemia at the second dose. Detailed information on complaints after each dose of the COVID-19 vaccine in the patient group according to underlying diagnosis was presented in Figure 2. The incidence of side effects was similar in both vaccine doses, regardless of the treatment agents used in patients with endocrine disorders (p>0.05).

Discussion

Several types of vaccines were produced rapidly against COVID-19, including mRNA and inactivated types as the most used ones. These vaccines were administered in adults initially and after safety approvals, vaccination schedules for adolescents and children were launched [2,3]. While the most frequently reported adverse event was local reactions at the vaccination site, systemic symptoms such as fatigue, headache, myalgia, and fever were also seen commonly in previous reports. Also, the incidence of side effects after COVID-19 vaccines was reported to be higher with mRNA vaccines than with inactivated ones [15,16]. We showed that the most common adverse event was local reactions in our both patient and control groups after COVID-19 vaccines. Thus, we found a higher ratio of complaints after the first dose of

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the mRNA vaccine than the inactivated type. Though, we have to note that our cohort had a small number of subjects in the inactivated vaccine group, which might influenced our results. The literature information on this subject belonged to adult age groups and initial results of vaccination studies in adolescents supported the safety of COVID-19 vaccines similarly [6]. However, more serious complications such as myocarditis and pericarditis were also reported in this age group [7,8]. The frequency of adverse events in the early post-vaccination period was reported as up to 60% and most of them were local events in pediatric studies [17-19]. All these data were obtained from healthy children, and the side-effect profile of these vaccines in pediatric patients with chronic diseases is not yet clearly known. Our results were comparable with these reports, showing a similar adverse event incidence after COVID-19 vaccines in patient and control groups. Also, we demonstrated that exposure to adverse events at the first dose did not affect the frequency of it at the second dose of COVID-19 vaccines in patients with endocrinological disorders.

The endocrine system was thought to be affected by COVID-19 vaccines [11,12]. However, the overall benefits of this immunization were accepted to outweigh the risk of adverse events. But the questions are still unresolved regarding the frequency of COVID-19 vaccine-related side effects in patients with an endocrinopathy [12]. In addition to the adverse events seen in the general population, further complications such as interstitial lung disease were reported in several patients with autoimmune diseases, particularly after the inactivated vaccine. Also, exacerbation of the underlying disease was one of the important problems encountered after COVID-19 vaccination [13]. In light of this information, concerns rose that whether COVID-19 vaccines cause different and severe adverse events in children and adolescents with chronic diseases. In a recent study, Haşlak *et al.* [20] found a similar safety and side-effect profile of COVID-19 vaccines in adolescents with rheumatological diseases, including autoimmune ones, compared to healthy controls. They reported a rate of adverse events of approximately 40%, which were observed more frequently with the mRNA-type vaccine. Their results showed that adverse events in adolescents with chronic diseases were commonly mild, such as fatigue, myalgia, and reaction at the vaccine site, apart from the underlying disease or treatment regimens [20]. Our study confirmed these results with a similar adverse event profile and severity in adolescents with endocrinological disorders. The patient group did not have a different frequency of side effects in the early post-vaccination period than the healthy controls. In addition, whether an autoimmune state did not make a difference regarding the incidence of events in each dose of vaccines. This outcome can support the idea that autoimmune disorders in endocrinology that do not treated by immunomodulator drugs, result in similar immune reactions as seen in non-autoimmune conditions. But further molecular and clinical studies should focus on this issue investigating the possible effects of these vaccines on autoimmunity and autoimmune diseases. On the other hand, the distribution of complaints varied among patients regarding underlying diagnoses. For example, we observed glycemic changes in some diabetic individuals. This can be explained by the fact that inflammatory responses influence insulin sensitivity, causing a fluctuation in blood glucose levels, but also by the individual variabilities in glycemic controls of patients with diabetes.

Despite the safety of vaccines, a small number of reported severe complications such as acute respiratory failure, sensorineural hearing loss, myocarditis, or thromboembolic events after COVID-19 vaccines, especially with the mRNA type, are pushing patients away from immunization programs and contribute to the vaccine hesitancy among populations [21-24]. However, we found that endocrine diseases did not increase the incidence of severe reactions to require hospitalization in both vaccine types and doses. This finding was similar to a previous report showing severe reactions in only two of 223 adolescents with rheumatological problems who received the mRNA vaccine [20]. Hence, we think that these results are valuable to diminish the concerns about the safety of COVID-19 vaccines in adolescents with endocrinological disorders. Nevertheless, our results reflected the adverse event profile of the early period after vaccination and there is a need for studies to evaluate the long-term side effects, and also to show the efficacy of these vaccines by investigating immune response or antibody levels in specific patient groups.

We know that routine childhood vaccines are generally admitted as safe in children with endocrine disorders. In particular, it is a well-known fact that steroids can alter the immune system and reactions, and conflicting results about adverse events of these vaccines under steroid treatment were reported recently. Some authors found a history of steroid intake as a predictor of adverse reactions, nonetheless, short-term low-dose corticosteroid usage was shown to reduce reactogenicity after COVID-19 vaccines in another study [25,26]. Yet, there is no evidence that hormone replacement therapies, but not high as a treatment dose, reduce the efficacy of the COVID-19 vaccine or increase its side effects. We found that adverse events did not differ among treated or untreated patients with endocrinological disorders. Also, none of the patients under hydrocortisone replacement for adrenal insufficiency had a severe reaction. Our outcomes can be explained by the fact that most treatment agents used in these diseases are only replacement therapies for the missing hormone, not a new substance for the organism. It was suggested that patients with endocrinological problems should be included in the routine vaccination programs, but they should be followed closely in terms of complications that may develop specific to the disease. Some suggestions were made for these patients, such as close blood glucose monitoring in diabetic individuals, additional insulin dose administration when necessary, or increasing the steroid replacement dose in patients with adrenal insufficiency when fever and serious side effects develop [10]. All these recommendations were based on data from adult patients, and our study supported these reports. For example, some of our patients with diabetes had hyperglycemia or hypoglycemia within the early period after the COVID-19 vaccines, as explained above. Both our outcomes and previous literature data showed us the importance of a patient-based individualized approach after the administration of COVID-19 vaccines in patients with endocrinological problems.

Study Limitations

The main strength of our study was that this is the first study to investigate early adverse events after COVID-19 vaccines in adolescents with endocrinological disorders. Nevertheless, there are notable limitations. First of all, we observed the data with a questionnaire for past events, which could be affected by individual subjective responses. However, most of the studies on drug/vaccine adverse events use similar methods. As another limitation, our patient group was not homogenous and we could not evaluate the duration or dosage of the treatment regimens for endocrine diseases. Also, we did not assess the history of COVID-19 infection before the vaccination but the regulations in our country did not allow the administration of COVID-19 vaccines to infected subjects within six months after the infection. Lastly, the low number of individuals in subgroup analyses such as comparisons in terms of underlying endocrine diagnosis or vaccine types can make it difficult to interpret these results. Especially the small sample size in the inactivated vaccine group might influence our outcomes as discussed above. Hence, prospective studies with larger cohorts are needed on this subject to elucidate the complications of these vaccines in such special patient groups.

Conclusion

In conclusion, the incidence and severity of adverse events after available COVID-19 vaccines in our country were similar between adolescents with endocrinological disorders and healthy subjects. Adverse events were more frequent after the mRNA vaccine compared to the inactivated one, and the most common complaint was local reactions in both vaccine types. Endocrine disorders with and without autoimmunity showed similar side effect profiles. Treatment agents for endocrine diseases did not cause a difference in the incidence of adverse events. However, patients should be informed and followed closely for disease-specific complications.

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Authorship contribution: İME, İCE, and AA designed the research. All the authors conducted the study and data collection. İME, İCE, and AA analyzed the data and performed a literature search. İME wrote the paper draft and generated the tables and figures. All authors contributed to the critical revision of the manuscript and approved the final manuscript.

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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References

1. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics 2020;52:549-547.
2. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, Köse Ş, Erdinç FŞ, Akalın EH, Tabak ÖF, Pullukçu H, Batum Ö, Şimşek Yavuz S, Turhan Ö, Yıldırmak MT, Köksal İ, Taşova Y, Korten V, Yılmaz G, Çelen MK, Altın S, Çelik İ, Bayındır Y, Karaoğlan İ, Yılmaz A, Özkul A, Gür H, Unal S; CoronaVac Study Group. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213-222.
3. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Polack FP, Zerbini C, Bailey R, Swanson KA, Xu X, Roychoudhury S, Koury K, Bouguermouh S, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Yang Q, Liberator P, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Gruber WC, Jansen KU; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385:1761-1773.
4. Molloy EJ, Bearer CF. COVID-19 in children and altered inflammatory responses. Pediatr Res 2020;88:340-341.
5. Haslak F, Barut K, Durak C, Aliyeva A, Yildiz M, Guliyeva V, Varol SE, Cebeci SO, Aygun F, Varli YZ, Ozel A, Onan SH, Kocoglu U, Erol M, Karagozlu F, Ulug N, Dedeoglu R, Sahin S, Adrovic A, Oztunc F, Kasapcopur O. Clinical features and outcomes of 76 patients with COVID-19-related multi-system inflammatory syndrome in children. Clin Rheumatol 2021;40:4167-4178.
6. Hause AM, Gee J, Baggs J, Abara WE, Marquez P, Thompson D, Su JR, Licata C, Rosenblum HG, Myers TR, Shimabukuro TT, Shay DK. COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years - United States, December 14, 2020-July 16, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1053-1058.
7. Husby A, Hansen JV, Fosbøl E, Thiesson EM, Madsen M, Thomsen RW, Sørensen HT, Andersen M, Wohlfahrt J, Gislason G, Torp-Pedersen C, Køber L, Hviid A. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ 2021;375:e068665.
8. Truong DT, Dionne A, Muniz JC, McHugh KE, Portman MA, Lambert LM, Thacker D, Elias MD, Li JS, Toro-Salazar OH, Anderson BR, Atz AM, Bohun CM, Campbell MJ, Chrisant M, D'Addese L, Dummer KB, Forsha D, Frank LH, Frosch OH, Gelehrter SK, Giglia TM, Hebson C, Jain SS, Johnston P, Krishnan A, Lombardi KC, McCrindle BW, Mitchell EC, Miyata K, Mizzi T, Parker RM, Patel JK, Ronai C, Sabati AA, Schauer J, Sexson Tejtel SK, Shea JR, Shekerdemian LS, Srivastava S, Votava-Smith JK, White S, Newburger JW. Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults. Circulation 2022;145:345-356.
9. Rhee EJ, Kim JH, Moon SJ, Lee WY. Encountering COVID-19 as Endocrinologists. Endocrinol Metab (Seoul) 2020;35:197-205.
10. Ku CR, Jung KY, Ahn CH, Moon JS, Lee JH, Kim EH, Kwon H, Kim HK, Suh S, Hong S, Ha J, Roh E, Kim JH, Kim MK; Committee of Clinical Practice Guideline of the Korean Endocrine Society. COVID-19 Vaccination for Endocrine Patients: A Position Statement from the Korean Endocrine Society. Endocrinol Metab (Seoul) 2021;36:757-765.
11. Pezzaioli LC, Gatta E, Bambini F, Facondo P, Gava M, Cavadini M, Buoso C, Di Lodovico E, Rotondi M, Ferlin A, Cappelli C. Endocrine system after 2 years of COVID-19 vaccines: A narrative review of the literature. Front Endocrinol (Lausanne) 2022;13:1027047.
12. Zhao Y, Wu X. Influence of COVID-19 vaccines on endocrine system. Endocrine 2022;78:241-246.
13. Cairoli E, Espinosa G. Autoimmune diseases and vaccines against COVID-19. Decision making in uncertain scenarios. Med Clin (Barc) 2021;157:247-252.
14. Karayeva E, Kim HW, Bandy U, Clyne A, Marak TP. Monitoring vaccine adverse event reporting system (VAERS) reports related to COVID-19 vaccination efforts in Rhode Island. R I Med J (2013) 2021;104:64-66.
15. Riad A, Sağıroğlu D, Üstün B, Pokorná A, Klugarová J, Attia S, Klugar M. Prevalence and Risk Factors of CoronaVac Side Effects: An Independent Cross-Sectional Study among Healthcare Workers in Turkey. J Clin Med 2021;10:2629.
16. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, Sudre CH, Nguyen LH, Drew DA, Merino J, Hu C, Selvachandran S, Antonelli M, Murray B, Canas LS, Molteni E, Graham MS, Modat M, Joshi AD, Mangino M, Hammers A, Goodman AL, Chan AT, Wolf J, Steves CJ, Valdes AM, Ourselin S, Spector TD. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis 2021;21:939-949.
17. Alamer E, Alhazmi A, Qasir NA, Alamer R, Areeshi H, Gohal G, Qadri M, Hashem AM, Algaissi A. Side Effects of COVID-19 Pfizer-BioNTech mRNA Vaccine in Children Aged 12-18 Years in Saudi Arabia. Vaccines (Basel) 2021;9:1297.
18. Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, Li M, Lian X, Jiao W, Wang L, Shu Q, Wu Z, Zhao Y, Li Q, Gao Q. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:1645-1653.
19. Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Türeci Ö, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4501001 Clinical Trial Group. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med 2021;385:239-250.
20. Haslak F, Gunalp A, Cebi MN, Yildiz M, Adrovic A, Sahin S, Barut K, Kasapcopur O. Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: A single-center study. Int J Rheum Dis 2022;25:353-363.
21. Sessa M, Kragholm K, Hviid A, Andersen M. Thromboembolic events in younger women exposed to Pfizer-BioNTech or moderna COVID-19 vaccines. Expert Opin Drug Saf 2021;20:1451-1453.
22. Jeong J, Choi HS. Sudden sensorineural hearing loss after COVID-19 vaccination. Int J Infect Dis 2021;113:341-343.
23. Kewan T, Flores M, Mushtaq K, Alwakeel M, Burton R, Campbell J, Perry H, Al-Jaghbeer M, Abi Fadel F. Characteristics and outcomes of adverse events after COVID-19 vaccination. J Am Coll Emerg Physicians Open 2021;2:e12565.
24. King WW, Petersen MR, Matar RM, Budweg JB, Cuervo Pardo L, Petersen JW. Myocarditis following mRNA vaccination against SARS-CoV-2, a case series. Am Heart J plus 2021;8:100042.
25. Parida SP, Sahu DP, Singh AK, Alekhya G, Subba SH, Mishra A, Padhy BM, Patro BK. Adverse events following immunization of COVID-19 (Covaxin) vaccine at a tertiary care center of India. J Med Viro 2022;94(6):2453-2459.
26. Yang J, Ko JH, Baek JY, Hong J, Ha S, Lee B, Huh K, Cho SY, Kang CI, Chung DR, Kim YJ, Kang ES, Peck KR. Effects of Short-Term Corticosteroid Use on Reactogenicity and Immunogenicity of the First Dose of ChAdOx1 nCoV-19 Vaccine. Front Immunol 2021;12:744206.

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Table 1. The comparison of the two groups regarding the findings of the first dose administration of COVID-19 vaccines.

	Patient group (n=85)	Control group (n=75)	p
Age (years)	15.1 (13.9 – 17.0)	16.0 (14.7 – 16.8)	0.182
Female [n (%)]	46 (54.1%)	44 (58.7%)	0.563
BNT162b2 mRNA vaccine [n (%)]	77 (51.3%)	73 (48.7%)	0.105
Adverse event incidence [n (%)]	52 (61.2%)	45 (60.0%)	0.879
Local reactions [n (%)]	32 (37.6%)	31 (41.3%)	0.634
Systemic reactions [n (%)]	36 (42.4%)	30 (40.0%)	0.763
Both local and systemic reactions [n (%)]	16 (30.2%)	16 (35.6%)	0.692
Severe adverse events [n (%)]	2 (2.4%)	1 (1.3%)	1.000

Table 2. The comparison of the two groups regarding the findings of the second dose administration of COVID-19 vaccines.

	Patient group (n=77)	Control group (n=69)	p
Age (years)	15.1 (13.8 – 17.0)	16.0 (14.7 – 16.8)	0.132
Female [n (%)]	43 (55.8%)	38 (55.1%)	0.925
BNT162b2 mRNA vaccine [n (%)]	70 (90.9%)	68 (98.6%)	0.066
Adverse event incidence [n (%)]	46 (59.7%)	45 (65.2%)	0.495
Local reactions [n (%)]	33 (42.9%)	29 (42.0%)	0.919
Systemic reactions [n (%)]	34 (44.2%)	31 (44.9%)	0.925
Both local and systemic reactions [n (%)]	18 (23.4%)	15 (21.7%)	0.813
Severe adverse events [n (%)]	1 (1.3%)	2 (2.9%)	0.603

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Table 3. The distribution of adverse events observed after COVID-19 vaccines.

Adverse events	The first dose of the BNT162b2 mRNA vaccine		The first dose of the inactivated vaccine		The second dose of the BNT162b2 mRNA vaccine		The second dose of the inactivated vaccine	
	Patients (n=77)	Controls (n=73)	Patients (n=8)	Controls (n=2)	Patients (n=70)	Controls (n=68)	Patients (n=7)	Controls (n=1)
Local reactions	31 (40.3%)	31 (42.5%)	1 (12.5%)	0 (0%)	32 (45.7%)	29 (42.6%)	1 (14.3%)	0 (0%)
Fever	13 (16.9%)	8 (11.0%)	1 (12.5%)	0 (0%)	13 (18.6%)	11 (16.2%)	1 (14.3%)	0 (0%)
Myalgia	14 (18.2%)	15 (20.5%)	1 (12.5%)	0 (0%)	11 (15.7%)	15 (22.1%)	2 (28.6%)	0 (0%)
Fatigue	16 (20.8%)	15 (20.8%)	2 (25.0%)	0 (0%)	14 (20.0%)	20 (29.4%)	0 (0%)	0 (0%)
Sore throat	2 (2.6%)	3 (4.1%)	0 (0%)	0 (0%)	3 (4.3%)	3 (4.4%)	0 (0%)	0 (0%)
Headache	7 (9.1%)	4 (5.5%)	0 (0%)	0 (0%)	1 (1.4%)	4 (5.9%)	0 (0%)	0 (0%)
Arthralgia	5 (6.5%)	4 (5.5%)	1 (12.5%)	0 (0%)	2 (2.9%)	2 (2.9%)	1 (14.3%)	0 (0%)
Cough	3 (3.9%)	2 (2.7%)	0 (0%)	0 (0%)	3 (4.3%)	1 (1.5%)	0 (0%)	0 (0%)
Vomiting	3 (3.9%)	1 (1.4%)	0 (0%)	0 (0%)	2 (2.9%)	2 (2.9%)	0 (0%)	0 (0%)
Abdominal pain	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash	0 (0%)	2 (2.7%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)
Hyperglycemia	7 (9.1%)	0 (0%)	1 (12.5%)	0 (0%)	4 (5.7%)	0 (0%)	0 (0%)	0 (0%)
Hypoglycemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Menstrual irregularity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)
Chest pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)

Table 4. The comparison of patients with endocrine disorders according to the autoimmune origin of their diseases.

		Autoimmune diseases (n=48)	Non-autoimmune diseases (n=37)	p
Age (years)		14.9 (13.9 – 17.0)	15.2 (13.8 – 17.1)	0.940
Female [n (%)]		28 (58.3%)	18 (48.2%)	0.374
The first dose (n=85)	**BNT162b2 mRNA vaccine [n (%)]**	42 (87.5%)	35 (94.6%)	0.457
	Adverse event incidence [n (%)]	29 (60.4%)	23 (62.2%)	0.870
	Local reactions [n (%)]	16 (33.3%)	16 (43.2%)	0.350
	Systemic reactions [n (%)]	22 (45.8%)	14 (37.8%)	0.460
	Both local and systemic reactions [n (%)]	9 (18.8%)	7 (18.9%)	0.984
	Severe adverse events [n (%)]	0 (0%)	2 (5.4%)	0.187
		Autoimmune diseases (n=43)	**Non-autoimmune diseases (n=34)**	**p**
The second dose (n=77)	**BNT162b2 mRNA vaccine [n (%)]**	38 (88.4%)	32 (94.1%)	0.455
	Adverse event incidence [n (%)]	25 (58.1%)	21 (61.8%)	0.747
	Local reactions [n (%)]	17 (39.5%)	16 (47.1%)	0.508
	Systemic reactions [n (%)]	20 (46.5%)	14 (41.2%)	0.640
	Both local and systemic reactions [n (%)]	9 (20.9%)	9 (26.5%)	0.568
	Severe adverse events [n (%)]	0 (0%)	1 (2.9%)	0.442

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Figure 1. The incidence of adverse events after each type and dose of COVID-19 vaccines in patient and control groups

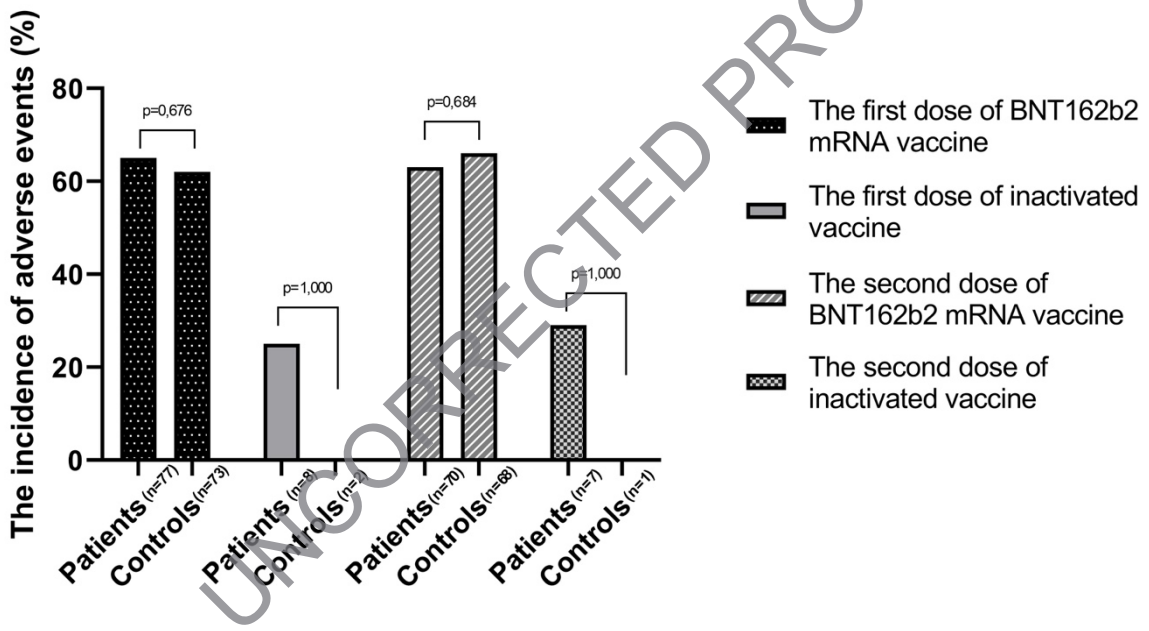
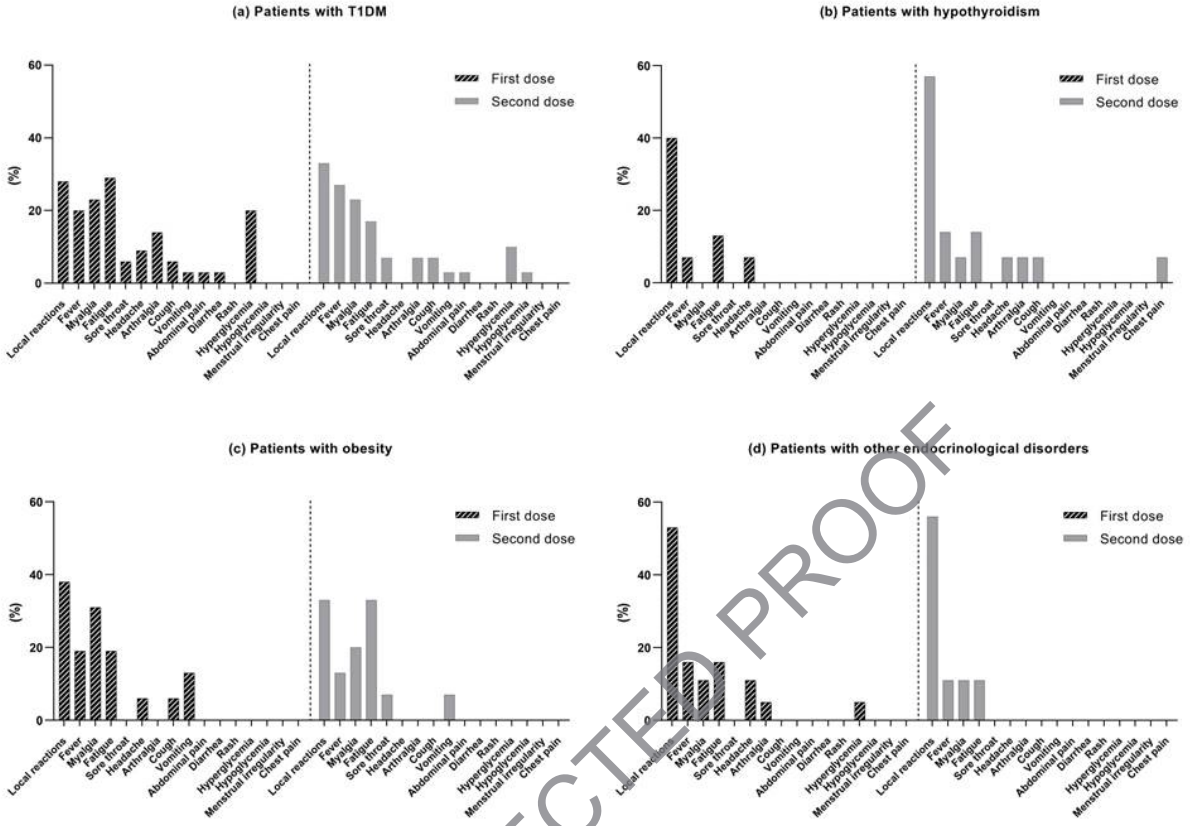


Figure 2. The distribution of adverse events in each dose of COVID-19 vaccines in the patient group, regarding the underlying diagnosis; (a) patients with type 1 diabetes mellitus (T1DM), (b) patients with hypothyroidism, (c) patients with obesity, (d) patients with other endocrinological disorders



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