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Survey of glucocorticoid dose escalation in patients with adrenal insufficiency during the peri-COVID-19 vaccination period

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Abstract. There is uncertainty regarding the need for COVID-19 peri-vaccination glucocorticoid coverage in patients with adrenal insufficiency. In this survey conducted in a single tertiary medical institution, 167 consecutive outpatients taking physiological glucocorticoids because of adrenal insufficiency were included. The patients declared if they developed an adrenal crisis after vaccination, and the amount and duration of an increase in their glucocorticoid dosage, if any. None of the patients without preventive glucocorticoid increase suffered an adrenal crisis after COVID-19 vaccination. Only 8.3% (14 cases) and 27.5% (46 cases) of the patients needed to escalate the dose of glucocorticoids when systemic symptoms appeared after the first and second injections, respectively. Glucocorticoids were increased in patients <60 years of age more than in patients ≥60 years of age at the time of both the first (p = 0.026) and second injections (p = 0.005). Sex and the causes of adrenal insufficiency were not associated with the frequency of the patients who needed glucocorticoid dose escalation. In the cases with increased glucocorticoids, the median dosage for escalation was 10 mg (hydrocortisone equivalent). In conclusion, even without prophylactic glucocorticoid administration, adrenal crisis did not occur during the peri-COVID-19 vaccination period. The dose escalation of steroid was more frequent in younger patients following the second vaccination. Careful monitoring of adverse effects and the appropriate management of glucocorticoids when necessary are essential following COVID-19 vaccinations.

Key words: COVID-19, Vaccination, Adrenal insufficiency, Steroid cover

THE GLOBAL SPREAD of novel coronavirus disease 2019 (COVID-19) poses a public health threat, while also changing the nature of society and people's values. In addition to treating COVID-19, medical fields other than infectious diseases must also consider COVID-19 and the complications associated with it.

In endocrinology, clinicians must focus on adrenal insufficiency in the COVID-19 era. Adrenal insufficiency refers to the impaired production of glucocorticoids/mineralocorticoids by the adrenal cortex, and is classified into three major categories according to the cause: primary, secondary, and tertiary [1]. Adrenal insufficiency is not rare; the estimated prevalence of primary and secondary adrenal insufficiency is 93–140 and 150–280 per million, respectively [2]. Regardless of the pathogenesis, patients with adrenal insufficiency need glucocorticoid replacement therapy, and adrenal crisis is a life-threatening emergency for these patients [3]. When such patients encounter physical stress such as surgery or infection, a supraphysiologic "stress dose" glucocorticoid administration is necessary to avoid a crisis. Hydrocortisone is the first choice for glucocorticoid replacement therapy, even in acute illness, because it provides a short-acting glucocorticoid effect with mineralocorticoid activity.

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Currently, vaccination against COVID-19 has increased rapidly. Consequently, several vaccines are available for use and provide a promising approach to improving COVID-19 infection control, worldwide. However, this vaccination sometimes causes several adverse reactions, such as tiredness, fever, and muscle pain [4]. These adverse reactions can cause physical stress and may lead to adrenal crisis in patients undergoing glucocorticoid replacement therapy. Therefore, the appropriate dose and timing of steroid coverage need to be determined.

The Pituitary Society surveyed its members' plans for glucocorticoid management in patients with adrenal insufficiency before and after COVID-19 vaccination. The results of this survey were based on the opinion of pituitary diseases experts, showing that 64% do not recommend an automatic glucocorticoid dose increase with vaccine administration [5]. A statement from the European Society of Endocrinology recommended careful monitoring after vaccination for the optimization of glucocorticoid dosing in case of systemic side effects [6]. This indicates that there is no need to routinely escalate the precautionary dose of glucocorticoids in patients with adrenal insufficiency at the time of vaccination against COVID-19. However, it is not clear whether the above-mentioned expert opinion and statement are consistent with the actual situation of steroid coverage in patients with glucocorticoid replacement. Maguire *et al.* reported five cases of adrenal insufficiency that led to an actual or incipient adrenal crisis requiring parenteral hydrocortisone within 24 hours of receiving the first ChAdOx1 SARS-CoV-2 vaccination [7]. They recommended increasing the glucocorticoid dosage only when the patients experienced any symptoms after receiving their COVID-19 vaccination. The adrenal crisis was also reported after BNT162b2 mRNA COVID-19 vaccination in a patient with hypopituitarism [8]. The authors of the case report recommended dose escalation of glucocorticoid is probably needed if a patient is experiencing any symptoms after COVID-19 vaccination.

We surveyed whether patients receiving steroid replacement therapy had increased the dose of hydrocortisone after COVID-19 vaccination, the actual amount increased, and the duration of administration. We also investigated the characteristics of patients requiring dose escalation. These results may serve as a reference for deciding which patients with adrenal insufficiency should be administered an increased dose of steroid at the time of COVID-19 vaccination, the dosage, and the duration of increase.

Material and Methods

Patients

This study was approved by the ethics committee of the Kobe University Graduate School of Medicine (Approval No. 1685). We interviewed 167 consecutive outpatients with adrenal insufficiency due to any cause, including hypopituitarism and adrenal diseases, at Kobe University Hospital between July 2021 and December 2021. Written consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used. The patients belonged to a population that was vaccinated under the usual COVID-19 vaccination schedule in Japan, and no special consideration was given to patients with adrenal insufficiency. The patient characteristics are described in Table 1. All the patients were taking a physiological dose of glucocorticoids [9]. The usual glucocorticoid dose (hydrocortisone equivalent) classified by the cause of adrenal insufficiency were as follows; hypopituitarism: 1.5% [5 mg], 42.7% [10 mg], 43.4% [15 mg], 11.8% [20 mg], and 0.7% [25 mg] (median 15 mg), primary adrenal insufficiency: 8.0% [5 mg], 16.0% [10 mg], 36.0% [15 mg], 32.0% [20 mg], and 8.0% [25 mg] (median 15 mg), and others: 83.3% [10 mg] and 16.7% [20 mg] (median 10 mg). The glucocorticoid replacement dosage under normal conditions was significantly different between patients with hypopituitarism and primary adrenal insufficiency ($p = 0.0027$).

These patients were educated in escalating steroid doses in times of physiological stress and were instructed to take the same action when systemic adverse reactions appeared during the peri-COVID-19 vaccination period. When taking glucocorticoids other than hydrocortisone, the dose of glucocorticoids has been shown as the hydrocortisone equivalent. We excluded those patients who received a supra-physiological dose of glucocorticoids. All the patients had received two doses of an mRNA COVID-19 vaccine (BNT162b2; Pfizer-BioNTech, or mRNA-1273; Moderna). In line with the Pituitary Society's majority opinion and the European Society of Endocrinology's statement mentioned above, attending physicians explained to these patients that prophylactic glucocorticoids were not necessary before COVID-19 vaccination. Only when the patients felt physical stress or the need to increase glucocorticoids due to the adverse reactions of the vaccine, such as fever and fatigue, were they instructed to increase the hydrocortisone dose in proportion to the stress. We followed the hormone replacement method according to the Endocrine Society's guidelines [10]; in particular, glucocorticoid replacement was directed according to the guidelines for adrenal insufficiency [9].

Table 1 Clinical characteristics

Total Number (*n*)		167
Gender (*n*, [%])		Males 82 [49.1] and females 85 [50.9]
Age (median, [range])		60 [21–88]
Dosage of glucocorticoid replacement under normal conditions* (*n*, [%])		5 mg; 4 [2.4] 10 mg; 67 [40.1] 15 mg; 68 [40.7] 20 mg; 25 [15.0] 25 mg; 3 [1.8]
Causes of adrenal insufficiency (*n*)		
Hypopituitarism	Pituitary/hypothalamus tumor (including post-operative hypopituitarism)	56
	Acquired isolated ACTH deficiency	18
	Rathke's cleft cyst	17
	Hypophysitis	15
	Congenital pituitary hormone deficiency	10
	Post radiation therapy	6
	Sheehan's syndrome	5
	Empty sella	4
	Apoplexy	3
	Others	2
	Total	136
Primary adrenal insufficiency	Addison's disease	16
	Congenital adrenal hyperplasia	8
	Adrenal hypoplasia congenita	1
	Total	25
Others	Steroid withdrawal syndrome	6
	Total	6

* Doses converted to hydrocortisone equivalents.

We interviewed the patients to determine if they had increased the dose of hydrocortisone as steroid cover and if they had experienced severe adverse reactions such as immediate allergic reaction, including anaphylactic shock. In cases where hydrocortisone was increased, we enquired about the amount of additional glucocorticoid and the duration of the increase. We also interviewed patients about the life-threatening complications of adrenal crisis (hypotension, consciousness, and abdominal symptoms such as nausea, *etc.*) and emergency room visits due to any symptoms after vaccination.

Statistical analysis

Statistical analyses were performed using JMP Statistical Database Software version 12·2·0 (SAS Institute, Cary, NC). Fisher's exact test or Pearson's chi-squared test were performed, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

None of the patients suffered severe adverse reactions, such as an immediate allergic reaction or adrenal crisis, after either of the two doses of the vaccine. However, 14 and 46 patients (8.3% and 27.5%, respectively) needed to elevate the glucocorticoid dose when systemic symptoms appeared during the first and second injections. Regarding the initiation of dose escalation, 9 out of 14 patients (64.3%) and 18 out of 46 patients (39.1%) started the escalation of glucocorticoid dose on the day of vaccination at the first and second injection, respectively.

Systemic symptoms of the reason for escalating the steroid dose were as follows: first injection; general malaise in 9 patients, fever in 6 patients, myalgia in 3 patients, headache in 2 patients, and unspecified in 1 patient, and second injection; general malaise in 28 patients, fever in 27 patients, myalgia in 7 patients, headache in 7 patients, and unspecified in 3 patients.

The patients who increased the glucocorticoid dose after the first injection needed an escalation of the glucocorticoid dose at the time of the second injection also (78.6%, $p < 0.001$). Neither sex nor the cause of the disease were associated with an increased glucocorticoid dose after either injection (sex: first injection [$p = 0.782$], 7.3% male and 9.4% female; second injection [$p = 0.230$], 23.2% male and 31.8% female) (cause of the disease: first injection [$p = 0.745$], 8.8% pituitary, 8.0% adrenal, and 0.0% others; second injection [$p = 0.637$], 28.7% pituitary, 20.0% adrenal, and 33.3% others) (Fig. 1A–D). However, when we divided the cohort into those above and below the median age (60 years), we found that those below the median required glucocorticoid dose

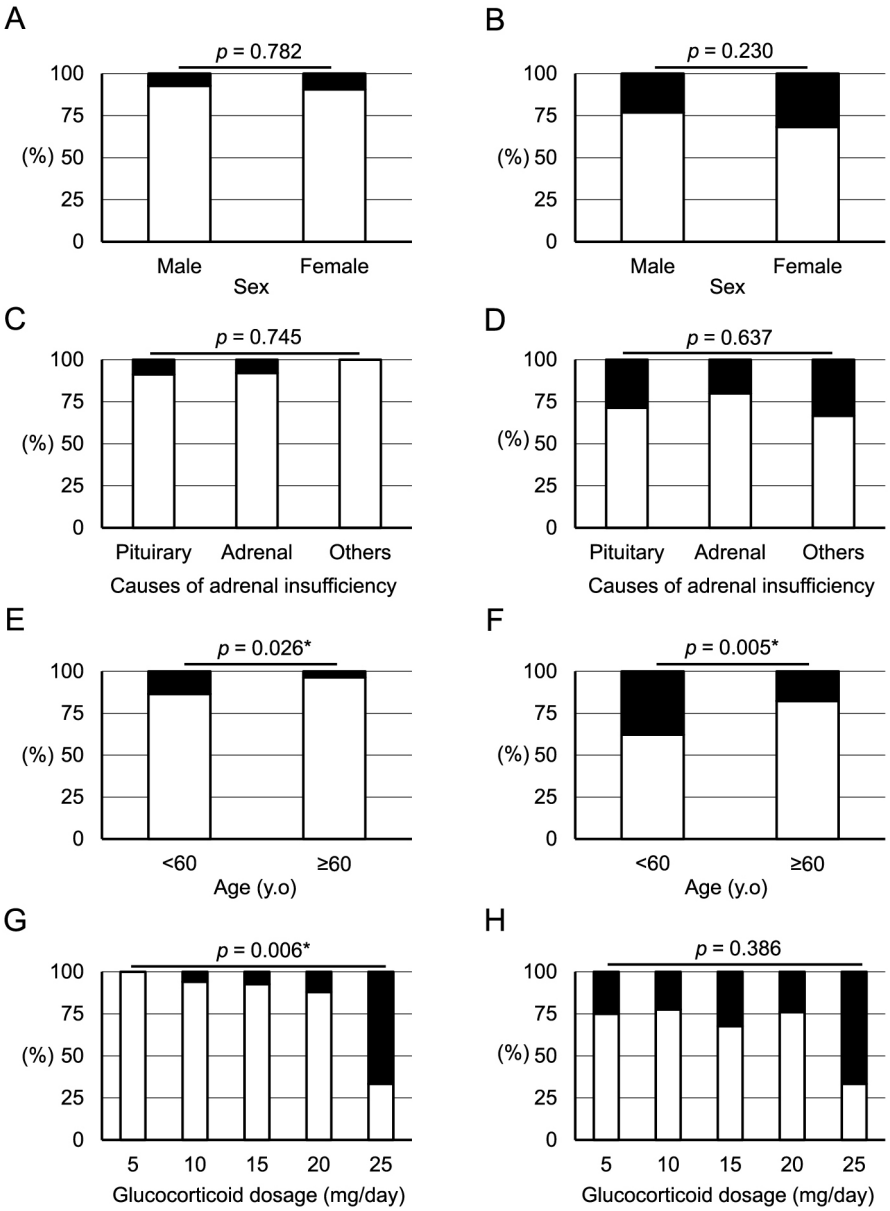

Fig. 1 Clinical characteristics of the patients who increased the dose of glucocorticoids after COVID-19 vaccination

Sex (A and B), the cause of adrenal insufficiency (C and D), the age of the patient (<60 years or ≥60 years) (E and F), and the dosage of glucocorticoid in the normal condition (doses are equivalent to that of hydrocortisone.) (G and H). First injection (A, C, E, and G) and second injection (B, D, F, and H). Sex (A and B) and the causes of adrenal insufficiency (C and D) did not show any differences in the patients who increased the glucocorticoid dosage after vaccination. Younger patients had a higher tendency to increase the dose of the glucocorticoid at the time of both the first and second injections, than did older patients (E and F). The ratio of patients with increased glucocorticoid levels differed significantly from those with glucocorticoid dosages as under normal conditions (G). However, no differences were observed after the second injection (H). Black columns indicate the proportion of the patients who increased the glucocorticoid doses.

Table 2 Details of the patients who increased their glucocorticoid dosage

		First injection		Second injection	
Number of cases out of 167			14		46
Duration of glucocorticoid escalation from vaccination	only on the day of vaccination		5		5
	day(s) after vaccination	1 day	6	1 day	29
		2 days	1	2 days	11
				3 days	1
		6 days	1		
		7 days	1		
Daily increase in the dose (mg) of glucocorticoid (median, [quartile range])*		10 [6.3–20]		10 [6.3–16.3]	

* Doses converted to hydrocortisone equivalents.

escalation after both the first and second injections more frequently than those above the median (first injection [p = 0.026], 12.5% [<60 years] and 3.5% [≥60 years]; second injection [p = 0.005], 36.6% [<60 years] and 17.7% [≥60 years]) (Fig. 1E and F). The proportion of patients who increased the dose of glucocorticoids was statistically different between the glucocorticoid dosages under normal conditions after the first injection. In particular, the rate of cases in which the glucocorticoid dose was increased was different between the 5 and 25 mg groups (first injection [p = 0.006], 0.0% [5 mg], 6.0% [10 mg], 7.4% [15 mg], 12.0% [20 mg], and 66.7% [25 mg]) (Fig. 1G). Such differences were not observed after the second injection (second injection [p = 0.386], 25.0% [5 mg], 22.4% [10 mg], 32.4% [15 mg], 24.0% [20 mg], and 66.7% [25 mg]) (Fig. 1H).

We analyzed the characteristics of the patients who increased the glucocorticoid dose after vaccination (Table 2). In most of these cases and for both injections, an escalation of glucocorticoid dosage was required for up to two days after vaccination. The total increased dosage varied because of the duration, but the mean daily increase in glucocorticoid dosage was only 10 mg, after both injections. The daily increase in the glucocorticoid dosage did not correlate with sex, age, causes of adrenal insufficiency (pituitary, adrenal, and others), or the dose of glucocorticoid under normal conditions (data not shown).

Discussion

In this study, none of the patients taking a physiological dose of glucocorticoids prophylactically increased the glucocorticoid dosage before vaccination against COVID-19. Despite that, none had an adrenal crisis, indicating that it is not necessary to increase the glucocorticoid dosage on the day of vaccination. The proportion of patients who increased the amount of hydrocortisone was higher after the second injection than after the first, and mostly in petite older patients.

The frequency of adverse reactions due to COVID-19 vaccination tended to be higher after the second injection than after the first [11]. Our results matched the results of the surveillance regarding the tendency for adverse reactions [11]. This may be because cases prone to adverse reactions after the first injection may also tend to have adverse reactions to the second injection. In addition, patients who increased the dose after the first injection may have had a strong awareness of adverse reactions to vaccines and may therefore have increased the dose after the second injection as well. The frequency of adverse reactions was different between BNT162b2 and mRNA-1273 [11]. However, because of many missing data, our study could not compare the difference in the escalation of glucocorticoid between the types of vaccines.

Patients <60 years of age showed a higher rate of glucocorticoid replacement than those ≥60 years. Systemic adverse events were reported more often in younger vaccine recipients than in older vaccine recipients [12]. Our data matched the general tendency of the occurrence of systemic adverse events. The median age of our cohort was 60 years. A cohort with a large number of younger people, including children and adolescents, may need a slightly higher coverage dose of glucocorticoids. However, hydrocortisone dose escalation may be difficult with increasing age, possibly due to misunderstandings [13] or impaired cognitive function [14, 15]; this can be clarified by further investigation.

We did not evaluate any symptoms other than severe adverse reactions such as immediate allergic reaction; therefore, we could not exclude the possibility that older adults did not increase glucocorticoids properly. However, none of the patients in this study developed an adrenal crisis; therefore, there appears to be no necessity to increase the dose of steroids, at least not prophylactically.

After the first injection, the proportion of patients requiring an increased glucocorticoid dosage differed statistically from those with the normal glucocorticoid dosage; this was particularly evident in the 25 mg group since the 5 mg group, under normal conditions, did not require an escalation of steroid dosage. We speculate that the endogenous glucocorticoid secretion in the 5 mg group was maintained to some extent and steroid coverage may not have been necessary. On the other hand, the patients taking a dose of 25 mg a day may need elevated glucocorticoid levels at the time of symptomatic adverse reactions after vaccination due to significant cortisol hyposecretion. At the second injection, the proportion of patients who increased glucocorticoid did not differ from that with glucocorticoid dosages under normal conditions. For patients taking 25 mg a day, the proportion of patients who increased glucocorticoid was similar between the first and second injection. However, the proportion of cases with escalating glucocorticoid dosage increased in the second injection in the ≤20 mg group. The need for glucocorticoid dosage may have increased in the group receiving ≤20 mg because the adverse reactions were more severe in the second vaccination than in the first. There was no evidence of a difference between the glucocorticoid dosages under normal conditions. However, since only a small number of patients took doses of 5 mg/day and 25 mg/day, these results are not enough to be able to draw a definite conclusion.

In our survey, none of the patients with adrenal insufficiency experienced adrenal crisis without a causative escalation of glucocorticoids. Thus, a uniform causative increase in glucocorticoids for adverse symptoms during the peri-COVID-19 vaccination period might not be necessary for patients with adrenal insufficiency. However, the results do not rule out the possibility that adrenal crisis could have occurred if the patients who increased their glucocorticoid dosage had not been properly supplemented. The third and subsequent COVID-19 vaccinations are expected shortly, and the escalation of glucocorticoid dosages for these vaccinations is an issue for further study.

Careful monitoring after COVID-19 vaccination and taking proper stress doses are considered appropriate responses for preventing adrenal crisis. However, the effect of this increased steroid dose on antibody titers is a subject for further study.

The results of this study may serve as a basis for vaccinations other than COVID-19 and when mRNA vaccines may be developed for other diseases in the future. It is not necessary to increase the prophylactic dose of glucocorticoids to prevent an adrenal crisis at the time of vaccination in patients with adrenal insufficiency, unless deemed necessary by the occurrence of adverse reactions after vaccination. The relationship between the need for a steroid cover and vaccinations other than against COVID-19 is also an issue for further, more extensive study.

In conclusion, we have shown that adrenal crisis did not occur in patients with adrenal insufficiency even without a prophylactic increase in the steroid dose after the COVID-19 vaccination. While this study did not examine a large number of patients, the result might support the adequacy of several statements [5, 6]. However, our study showed that in some patients, especially younger patients, or at the time of the second injection, the increased dose of glucocorticoid was more frequently required due to systemic adverse effects. Therefore, careful monitoring of the patient's symptoms after vaccination is essential to determine if an increase in glucocorticoid is needed.

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Disclosure Summary

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Author Contributions

Data collection: HB, MY, MT, YS, YO, KH, SN, MS, GI, and HF

Data analysis and interpretation: HB, KK, ST, SU, NY, and HS

Drafting the manuscript: HB and HF

Supervision of the study and critical revision of the article: HF and WO

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