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Impact of coronavirus disease 2019 on medical practice in endocrine and metabolic diseases in Japan: a nationwide surveillance study conducted by the Japan Endocrine Society

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Abstract. We investigated the impact of the Coronavirus disease 2019 (COVID-19) pandemic on the management of endocrine and metabolic disorders in Japan. We conducted a cross-sectional nationwide questionnaire survey targeting board-certified endocrinologists under the auspices of the Japan Endocrine Society. The questionnaire consisted of multiple-choice questions and open-ended responses. Out of approximately 2,700 specialists, 528 (19.5%) opted to participate, suggesting a high level of interest in COVID-19 management among endocrinologists. The study found that almost half of participants had encountered cases of endocrine and metabolic disorders following COVID-19 infection or vaccination. Conditions related to thyroid diseases, glucose metabolism disorders/diabetes, and hypothalamic-pituitary disorders were particularly prevalent. Diabetes and obesity were identified as having high rates of severe cases or fatalities due to COVID-19. The study also highlighted challenges in routine diagnosis and treatment, emphasizing the potential benefits of combining remote consultations with in-person visits to optimize the frequency of examinations and check-ups during infectious disease outbreak which disrupts access to healthcare providers. The insights obtained from this survey are expected to contribute to ensuring appropriate healthcare provision for patients with endocrine and metabolic disorders by using flexible consultation formats, particularly even in the conditions where medical access may be limited due to future outbreaks of emerging or re-emerging infectious diseases.

Key words: Coronavirus disease 2019 (COVID-19), Pandemic, Post COVID-19 condition (long COVID), Endocrine and metabolic diseases

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THE OUTBREAK of the coronavirus disease 2019 (COVID-19) has had a profound impact on the medical and healthcare fields. In the management of various endocrine and metabolic diseases, it has become important to address not only acute problems associated with COVID-19 but also medium to long-term problems related to the difficulties in the management of underlying diseases, complications, and a decline in quality of life in a broad sense. Given this background, the present study aims to elucidate the actual impact of COVID-19 on the diagnosis and treatment of endocrine and metabolic diseases in Japan. To achieve this goal, a nationwide survey targeting board-certified endocrinologist was conducted by the Japan Endocrine Society. We attempted to clarify the current situation and challenges in the clinical care of endocrinology and metabolism. There have been numerous studies on the impact of COVID-19, including its effects on the whole healthcare system [1-5], mental health care [6], medical education [7], cancer [8, 9], thyroid surgery [10-14], diabetes mellitus [15], and more. However, there has been no precedent for a large-scale nationwide survey targeting specialists in endocrinology and metabolism, with a focus on the impact of COVID-19 on endocrine and metabolic disease management. The analysis of the issues related to the impact of COVID-19 on endocrine and metabolic disease management has the potential to provide significant insights for establishing a rational and scientifically-informed response to future pandemics of emerging or re-emerging infectious diseases, thus contributing to the development of a more robust healthcare system. In addition, it is possible that underlying unresolved problems in the routine clinical care of endocrine and metabolic diseases will become clear from this kind of study, which could lead to improvements in the quality of healthcare.

Materials and Methods

Study design and participants

This study was a cross-sectional questionnaire survey whose primary purpose was to investigate the actual status during the period, for which a full survey was employed. The target population was approximately 2,700 specialists in endocrinology and metabolism (internal medicine) certified by the Japan Endocrine Society. No special exclusion criteria were set for this survey. From the secretariat of the Japan Endocrine Society, a request for responses to the questionnaire was sent *via* email to the target population on February 10, 2023. Simultaneously, the request was also posted on the Japan Endocrine Society's website. Two additional reminders requesting responses to the questionnaire were sent *via* email. The response period was from February 10, 2023 to March 3, 2023 (22 days).

Questionnaire

The structure of the questionnaire is as follows: 1) Basic information on the participants was obtained, including Japan Endocrine Society membership number, years of working as a physician, name of the institution they belonged to, whether they were responsible for the endocrinology department at their institution, and the size of the institution (number of beds and approximate number of patients in the relevant department). Since Japan Endocrine Society membership numbers were provided, duplicate responses could be avoided. 2) Subjects were asked about the effects of COVID-19 pandemic on the practice of endocrinology and metabolism by diseases and the reasons for these effects. They answered the questionnaire according to seven classifications of diseases: (1) general practice of endocrine and metabolic diseases and post-acute sequelae of COVID-19 infection (long COVID); (2) hypothalamic-pituitary disorders; (3) thyroid diseases; (4) parathyroid diseases and osteoporosis; (5) adrenal diseases and hypertension; (6) diabetes and obesity; and (7) dyslipidemia and hyperuricemia. The questions were multiple-choice, except for some numerical response questions (years of working as a physician), and the "other" option was left open for participants to provide further details.

The questionnaire was developed in consultation with 18 members, including 15 physicians and a statistician, led by the directors of the Japan Endocrine Society. Subsequently, 2–3 endocrinologists from each of the 7 facilities participating in this survey evaluated the draft for readability of the questionnaire, identity of interpretation, and ease of response, and adjustments were made accordingly.

The questionnaire form was created in Google Forms and information on this survey was posted on the Japan Endocrine Society website as well as emailed to the subjects. The information on this survey was also posted. The questionnaire contained 109 questions, and the estimated average response time was 20 minutes. The questionnaire is shown in the Supplementary Fig. 1 (English version) and Supplementary Fig. 2 (Japanese version).

Ethics

This survey was conducted in compliance with the Declaration of Helsinki (revised October 2013) and the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and Ministry of Economy, Trade and Industry Notification No. 1, 2021).

The ethical review of this survey was approved by The Ethics Committee of University of the Ryukyus for Medical and Health Research Involving Human Subjects, which is the main research institution, through a central collective review, and was conducted with the permission of the heads of all research institutions (University of the Ryukyus permission number: No. 2066).

Statistical analysis

All returned responses were considered valid responses, except for duplicate responses, which were judged by Japan Endocrine Society membership number. Summary statistics (mean, standard deviation, median, interquartile range, and range) were calculated for numerical responses, and frequency tabulations (number of response choices and percentage) was conducted for multiple-choice responses. We were unable to obtain direct information on the characteristics of non-respondents, so we decided to estimate the target population through sampling. To estimate the characteristics of target population through sampling from 2,700 individuals, ensuring a margin of error of 5% and a confidence level of 95%, a minimum of 337 surveys would be required. Therefore, we randomly sampled 360 individuals and conducted confirmation of the facilities of these 360 individuals, as well as verification of the information about their facilities. The denominator for percentage calculation was the number of valid responses to the question. Among free-text responses, word responses (*e.g.*, free-text responses to the "other") were frequency-tabulated by reading and coding by two medical specialists. For questions with more than 50 short answers, word frequency tally, co-occurrence analysis, and correspondence analysis were conducted by text mining. For similar questions across domains, frequency tabulations were conducted after recoding to ensure commonality across domains. Text mining was performed on Japanese sentences. We made a word list of nouns, verbs and adjectives from the headlines using the Japanese language morphological analysis program ChaSen version 2.1 (Nara Institute of Science and Technology). The co-occurrence network analysis was performed on the extracted data. In the co-occurrence network chart, words with similar appearance patterns (*i.e.*, with high degrees of co-occurrence) are connected by edges. Thicker edges correspond to stronger co-occurrence. If words are not connected with edges, there is no strong co-occurrence. The color of each node represents sub-graphs, which means that the same color belongs to the same group. Edges between words belonging to different sub-graphs are represented by dotted lines. By considering words with strong co-occurrences and sub-graphs, the meaning of a particular word in the text can be interpreted.

All statistical analyses were conducted using SPSS version 24.0 for Windows and SPSS Text Analytics (IBM Japan, Ltd.).

Results

We investigated the impact of the COVID-19 pandemic on the management of endocrine and metabolic disorders in Japan, performing a nationwide cross-sectional questionnaire survey targeting endocrinologists who were board-certified by the Japan Endocrine Society.

We received responses from 528 out of approximately 2,700 endocrinologists, resulting in a 20% response rate. Not a small number of responses suggests a significant COVID-19 impact on the management of endocrine and metabolic diseases, along with a high level of interest among endocrinologists.

The median years of experience as physicians among the responding specialists were 22 years. In terms of the types of healthcare facilities where the participants worked, the response rate from participants working in clinics was lower, while the response rate from participants working in university hospitals and general hospitals was higher; 42% were affiliated with university hospitals, 42% with general city hospitals, and 15% with clinics. The fact that most of the respondents were physicians working in university hospitals or general city hospitals indicates their involvement in highly specialized endocrine and metabolism practice (Table 1).

Among the participants, 179 (34%) had experience diagnosing endocrine abnormalities in patients following COVID-19 vaccine administration (Table 2). The breakdown of endocrine abnormalities following COVID-19 vaccination was as follows: 137 participants (77%) had experienced abnormal findings in thyroid, 43 (24%) had abnormal findings in glucose metabolism, and 34 (19%) had abnormal findings in the hypothalamic-pituitary axis.

Additionally, 157 out of the 528 participants (30%) had experience diagnosing endocrine abnormalities in patients following COVID-19 infection. The breakdown of endocrine abnormalities in this group following COVID-19 was as follows: 83 participants (53%) had experienced abnormal findings in thyroid, 63 (40%) had abnormal findings in glucose metabolism, and 36 (23%) had abnormal findings in the hypothalamic-pituitary axis.

Almost half of the participants (249 out of 528; 47%) had experience diagnosing endocrine abnormalities in patients following COVID-19 vaccine administration and/or COVID-19 infection.

Furthermore, 253 participants (48%) had experience in

Table 1 Characteristics of survey respondents and target populations

	Respondents (n = 528)	Target population
Years of experience as a physician (year)		
Mean ± SD	23.6 ± 10.3	N/A
Median [IQR] (range)	22.0 [15.0–31.0]; (3–53)	N/A
Responsible for the endocrine and metabolic disease department (n, %)	257, 48.7%	N/A
Type of institution (n, %)		
Clinic	77, 14.6%	30.8%
City hospital	223, 42.2%	34.4%
University hospital	224, 42.4%	31.1%
Other (government, business, *etc.*)	4, 0.8%	3.6%
Bedded facility (n, %)	456, 86.4%	66.1%
More than 500 beds (n, % [of n = 456])	309, 67.8%	61.3%
400–499 beds	36, 7.9%	8.4%
300–399 beds	36, 7.9%	8.8%
200–299 beds	36, 7.9%	5.9%
100–199 beds	19, 4.2%	9.7%
20–99 beds	17, 3.7%	5.0%
1–19 beds	3, 0.7%	0.8%
Area (n, %)		
Hokkaido Region	11, 2.1%	2.5%
Tohoku Region	20, 3.8%	4.0%
Kanto Region	98, 18.6%	35.9%
Chubu Region	146, 27.7%	19.7%
Kinki Region	104, 19.7%	20.6%
Chugoku Region	20, 3.8%	4.5%
Shikoku Region	15, 2.8%	2.9%
Kyushu/Okinawa Region	84, 15.9%	9.9%
Unknown	30, 5.7%	0%

SD: standard deviation, IQR: inter-quartile range [25%, 75%], N/A: not available
The facilities of the target population: From the publicly available directory provided by the Japan Endocrine Society, 360 individuals were randomly sampled and identified the facilities using search engines.
The areas of the target population: The areas were extracted directly from the publicly available directory provided by the Japan Endocrine Society.
Areas in Japan: Japan was divided into eight regions (https://www.japan-guide.com/list/e1001.html).

treating "long COVID." The common symptoms in patients with long COVID which the participants had experienced were fatigue and malaise (88%), chronic cough (68%), taste disorder (42%), shortness of breath (34%), olfactory disorders (32%), and deficits in attention (27%). These symptoms may also be attributable to endocrine and metabolic disorders, such as thyroid dysfunction, adrenal insufficiency, and pituitary insufficiency. Therefore, patients are sometimes referred to an endocrinologist for specialized care and evaluation.

As many as 488 participants (92%) answered a binary question affirming that the rapid spread of COVID-19 after April 2020 had impact on changes in the clinical environment and the number of hospitalized patients with endocrine and metabolic disorders (Table 3). The breakdown of the changes showed that 391 participants (81%) started conducting telephone telemedicine, 318 (65%) made changes to the clinical environment such as waiting rooms and examination rooms, and 274 (56%) reduced the number of hospitalized patients. The initiation of video telemedicine remained at low rate (7.4%).

Hypothalamic-pituitary disorders

There were 223 participants (42%) who responded that COVID-19 pandemic had negative effects on the management of hypothalamic-pituitary disorders

Table 2 Abnormal endocrinological findings and sequelae related to the COVID-19 experienced

	Total (n = 528)
Experience of Endo-Abnorm after vaccine: yes (n, %)	179, 33.9%
Region in which abnormal findings were found (n, % [of n = 179])*	
Hypothalamic and Pituitary gland	34, 19.1%
Thyroid gland	137, 77.0%
Parathyroid gland	2, 1.1%
Adrenal gland	13, 7.3%
Pancreas and gastrointestinal tract	5, 2.8%
Gonads	3, 1.7%
Glucose metabolism	43, 24.2%
Other	4, 2.2%
Experience of Endo-Abnorm after COVID-19 infection: yes (n, %)	157, 29.7%
Region in which abnormal findings were found (n, % [of n = 157])*	
Hypothalamic and Pituitary gland	36, 22.9%
Thyroid gland	83, 52.9%
Parathyroid gland	2, 1.3%
Adrenal gland	14, 8.9%
Pancreas and gastrointestinal tract	3, 1.9%
Gonads	7, 4.5%
Glucose metabolism	63, 40.1%
Other	3, 1.9%
Experience of sequelae after COVID-19 infection: yes (n, %)	253, 47.9%
Experienced symptoms (n, % [of n = 253])	
Fatigue and malaise	224, 88.2%
Arthralgia	23, 9.1%
Myalgia	25, 9.8%
Cough	172, 67.7%
Sputum	55, 21.7%
Shortness of breath	85, 33.5%
Chest pain	18, 7.1%
Alopecia	37, 14.6%
Memory impairment	25, 9.8%
Concentration problems	68, 26.8%
Headache	45, 17.7%
Depression	47, 18.5%
Olfactory disturbances	80, 31.5%
Taste disorder	108, 42.5%
Palpitations	19, 7.5%
Diarrhea	9, 3.5%
Abdominal pain	7, 2.8%
Sleep disturbance	29, 11.4%
Muscle weakness	26, 10.2%
Other	7, 2.8%

Endo-Abnorm: endocrinological abnormalities
*: multiple-answer question

(Fig. 1). The breakdown of the negative effects on hypothalamic-pituitary disorders due to COVID-19 was as follows: experiencing cases requiring steroid coverage (43%), encountering cases where hospitalization was delayed or not possible (37%), and experiencing cases where necessary consultations and tests became

Table 3 Changes in medical practice patterns

	Total (n = 528)
Changes in medical practice patterns after COVID-19 (n, %)	
Yes	488, 92.4%
No	40, 7.6%
Details of changes in the form of medical treatment (n, % [of n = 488])	
Telephone telemedicine	391, 80.5%
Video telemedicine	36, 7.4%
Changed the hospital environment	318, 65.4%
Number of inpatients admitted to the hospital decreased.	274, 56.4%
Other (free comment)	22, 4.5%

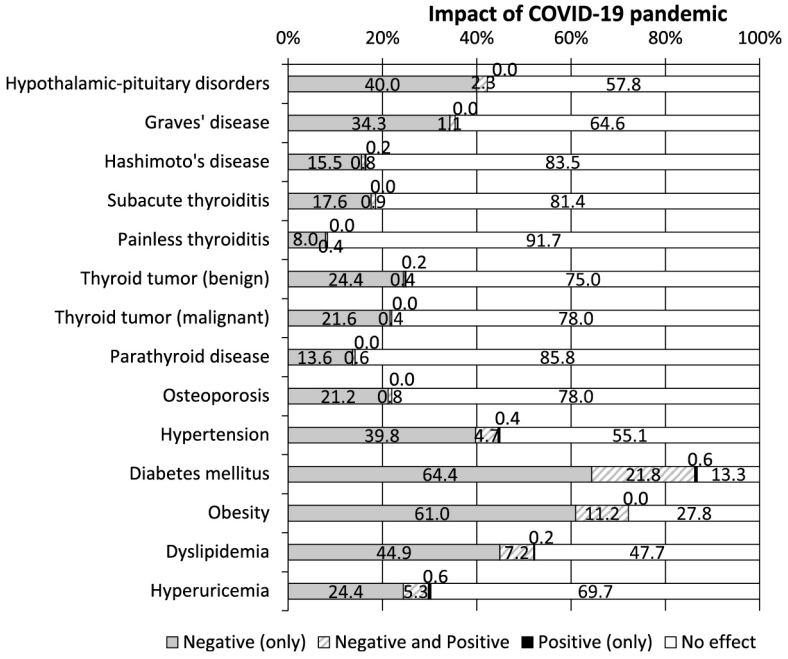


Fig. 1 The impact of COVID-19 pandemic on each endocrine disease area

The frequency of responses to the question, "How has COVID-19 pandemic affected your practice?" in each disease area: bar graph

Answers are chosen exclusively from the following four:

1) It had negative effects [Negative (only)]
2) There were both positive and negative effects [Negative and Positive]
3) It had positive effects [Positive (only)]
4) There was no effect [No effect].

insufficient due to extended visitation periods (35%) were ranked as the most prevalent (Table 4).

A decrease in the number of surgical cases of pituitary tumor was reported by 69 participants (13%), with the most common reason being restrictions in the operation of the operating room (65%).

In the management of patients with arginine vasopressin (AVP) deficiency (central diabetes insipidus), 24 participants (5%) reported that they had experienced difficulties in managing electrolytes. The main reasons included changes in the required dosage of desmopressin (29%), the occurrence of hyponatremia due to intravenous fluids administered for the treatment of COVID-19 (29%), and the inability to undergo necessary consultations and blood tests due to isolation (29%).

Furthermore, 82 participants (16%) faced challenges with steroid coverage. The primary reasons were fluctuations in the required steroid dosage (54%) and the onset of adrenal crisis (52%).

Twenty-nine participants reported experiencing

Table 4 Reasons for negative effect of COVID-19 on practice, by disease

Classification of diseases		Rank 1	Rank 2	Rank 3
Hypothalamic and Pituitary gland (negative effect: *n* = 220)	Reason	There were some patients in whom steroid coverage was required during COVID-19 infection	There were patients who were not able to be hospitalized or whose admission was delayed due to COVID-19 pandemic, even though they needed hospitalization	Insufficient monitoring through medical examinations due to prolonged intervals between visits
	n, %	94, 42.7%	82, 37.3%	78, 35.5%
Graves' disease (negative effect: *n* = 184)	Reason	Because it interfered with the continuation of drug therapy	Because it interfered with the detection and diagnosis of the disease	Because it interfered with oral radioiodine therapy
	n, %	112, 60.9%	67, 36.4%	32, 17.4%
Hashimoto's disease (negative effect: *n* = 82)	Reason	Because it interfered with the continuation of drug therapy	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the initiation of drug therapy
	n, %	64, 78.0%	24, 29.3%	7, 8.5%
Subacute thyroiditis (negative effect: *n* = 93)	Reason	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the continuation of drug therapy	Because it interfered with the initiation of drug therapy
	n, %	69, 74.2%	14, 15.1%	6, 6.5%
Painless thyroiditis (negative effect: *n* = 43)	Reason	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the continuation of drug therapy	Because it interfered with the initiation of drug therapy
	n, %	33, 76.7%	9, 20.9%	5, 11.6%
Thyroid tumor (benign) (negative effect: *n* = 128)	Reason	Because it interfered with the follow-up observation	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the surgical therapy
	n, %	87, 68.0%	49, 38.3%	23, 18.0%
Thyroid tumor (malignant) (negative effect: *n* = 115)	Reason	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the surgical therapy	Because it interfered with the follow-up observation
	n, %	63, 54.8%	53, 46.1%	45, 39.1%
Parathyroid disease (negative effect: *n* = 72)	Reason	Because it interfered with the detection and diagnosis of the disease	Because it interfered with surgical therapy	Because it interfered with the continuation of drug therapy
	n, %	44, 61.1%	22, 30.6%	16, 22.2%
Osteoporosis (negative effect: *n* = 112)	Reason	Because it interfered with the continuation of drug therapy	Because it interfered with the detection and diagnosis of the disease	Because it interfered with the initiation of drug therapy
	n, %	58, 51.8%	57, 50.9%	23, 20.5%
Hypertension (negative effect: *n* = 234)	Reason	Because many patients delayed seeing a doctor, getting diagnosed, or starting treatment	Because many patients were late in receiving medical examinations, diagnoses, and starting treatment	Because many patients had problems with weight loss Because many patients failed to visit the hospital
	n, %	133, 56.8%	129, 55.1%	98, 41.9%
Diabetes mellitus (negative effect: *n* = 452)	Reason	Because many patients had difficulty with exercise therapy	Because many patients had difficulty with diet therapy	Because many patients gained weight
	n, %	401, 88.7%	278, 61.5%	266, 58.8%
Obesity (negative effect: *n* = 378)	Reason	Because many patients had difficulty with exercise therapy	Because many patients had difficulty with diet therapy	Because many patients delayed seeing a doctor, getting diagnosed, and starting treatment
	n, %	360, 95.2%	277, 73.3%	147, 38.9%
Dyslipidemia (negative effect: *n* = 276)	Reason	Because the risk of dyslipidemia increased due to obesity, drinking alcohol, lack of exercise, *etc.*, as a result of home-based living	Because the patients avoided going to medical institutions and treatment intervention was delayed, although abnormal values were indicated in health checkups	Because the patients stopped seeing their doctors
	n, %	233, 84.4%	159, 57.6%	105, 38.0%
Hyperuricemia (negative effect: *n* = 157)	Reason	Because the risk of hyperuricemia increased due to obesity, drinking alcohol, overeating, *etc.*, as a result of home-based living	Because the patients avoided going to medical institutions and treatment intervention was delayed, although abnormal values were indicated in health checkups	Because the patients stopped seeing their doctors
	n, %	118, 75.2%	86, 54.8%	69, 43.9%

The rank is determined by the frequency of selected reasons (multiple choices allowed) for the negative effect of COVID-19 on practice, as reported by respondents who experienced such effect.

hypothalamic-pituitary-adrenal (HPA) axis abnormalities after vaccination, with more than half of the participants clearly stating a secondary etiology: 17 secondary, 1 primary, and 11 unknown. Twenty-six participants experienced HPA axis abnormalities after COVID-19 infection, with the etiology of all 17 participants who explicitly stated the etiology as being secondary.

Thyroid diseases

There were 187 participants (35%) who responded that COVID-19 pandemic had negative effects on the management of Graves' diseases (Fig. 1). The breakdown of the negative effects on Graves' disease due to COVID-19 pandemic was as follows: experiencing cases who had difficulties in continuing medication (61%) and experiencing cases with delayed diagnosis (36%) were ranked as the most prevalent (Table 4).

In the management of Graves' disease patients with COVID-19 infection, 86 participants (16%) reported that they had experienced difficulties. The main reasons included the inability to undergo necessary consultations and examinations (55%), the inability to prescribe necessary medications (37%), and a worsening of the condition due to the interruption of oral medication and disruptions in lifestyle habits (37%).

Similarly, in the management of Hashimoto's disease (hypothyroidism) patients with COVID-19 infection, 86 participants (16%) reported that they had experienced difficulties. The main reasons included the difficulties in continuing medications (78%) and the delay in diagnosis of the disease (29%).

In addition, there were some responses that COVID-19 pandemic had negative effects on the management of subacute thyroiditis, painless thyroiditis, benign thyroid tumors, and malignant thyroid tumors.

Parathyroid diseases and osteoporosis

There were 75 participants (14%) who responded that COVID-19 pandemic had negative effects on the management of parathyroid diseases (Fig. 1).

The breakdown of the negative effects on parathyroid diseases due to COVID-19 pandemic was as follows: experiencing cases with delayed diagnosis (61%) and experiencing cases who had obstacles in surgical treatment (31%) were ranked as the most prevalent (Table 4).

A decrease in the number of surgical cases of parathyroid disease was reported by 56 participants (11%), with the most common reason being restrictions in the operation of the operating room (62%).

In the management of calcium and phosphorus metabolism in patients contracting COVID-19 infection, only 8 participants (2%) reported they had experienced difficulties.

There were 116 participants (22%) who responded that COVID-19 pandemic had negative effects on the management of osteoporosis (Fig. 1).

The breakdown of the negative effects on osteoporosis due to COVID-19 pandemic was as follows: experiencing cases who had difficulties in continuing medication (58%) and experiencing cases with delayed diagnosis (57%) were ranked as the most prevalent.

In addition, there were as many as 285 participants (54%) who responded that COVID-19 pandemic had negative effects on the management of musculoskeletal health.

Adrenal diseases and hypertension

There were 235 participants (45%) who responded that COVID-19 pandemic had an adverse effect on the management of hypertension (Fig. 1).

The breakdown of the negative effects on hypertension due to COVID-19 pandemic was as follows: experiencing cases who had obstacles in medical treatment (initiation, dose adjustment, and continuation) (57%) and experiencing cases with delayed diagnosis (55%) were ranked as the most prevalent (Table 4).

Regarding the treatment of adrenal disorders, 118 participants (22%) reported a decrease in the screening frequency for primary aldosteronism. The most prominent reason was the decrease in patient visits, which accounted for about 86%.

Similarly, there were 59 participants (11%) who reported a decrease in treating adrenal tumors. The main reasons included a decrease in opportunities for imaging tests (50%) and a decrease in opportunities for detailed examinations (38%).

A decrease in the number of surgical cases of adrenal tumor was reported by 70 participants (13%), with the main reasons being restrictions on operating room usage (55%) and a decrease in patient visits (41%).

On the other hand, 82 participants (16%) reported an increase in the frequency of treating adrenal insufficiency due to COVID-19 pandemic. The main reason cited was that COVID-19 itself was a cause of adrenal insufficiency, mentioned by 55% of the participants in a high proportion.

Regarding sick day rules for adrenal insufficiency, 21% of the participants advised an increase in glucocorticoid (GC) replacement dose for their patients with adrenal insufficiency if COVID-19 infection was identified regardless of symptoms; 26% advised to increase the dose depending on symptoms; and more than half did not give specific instructions for COVID-19 infection. And in the case of COVID-19 vaccination, 5% of participants advised to increase the dose even if there were no adverse reactions, 68% advised to increase the dose if

there were adverse reactions, and 26% did not instruct to increase the dose. Of the participants who indicated a GC dose increase at the time of vaccination even in the absence of an adverse reaction, more than half (14 participants) were participants who also advised an increase at the time of COVID-19 identification in the absence of symptoms.

Diabetes mellitus and obesity disease

There were as many as 455 participants (86%) who responded that COVID-19 had negative effects on the management of diabetes mellitus (Fig. 1).

The major negative effects on the management of diabetes mellitus due to COVID-19 pandemic were as follows: experiencing cases who had obstacles to exercise therapy (89%), obstacles to dietary therapy (62%), weight gain (59%), and dealing with delays in patient visits, diagnoses, and treatment initiation (57%) (Table 4).

The spread of the COVID-19 led to further effects: extended patient appointment intervals (66%), introduction of telephone telemedicine (62%), reduction or cancellation of activities like foot care, diabetes classes, and patient meetings (55%), as well as a decrease in hospital admissions for treatment of diabetes mellitus (55%).

Many of the participants encountered diabetes mellitus patients with moderate cases of COVID-19 infection that required interventions like oxygen therapy or hospitalization (56%), severe cases of COVID-19 infection necessitating intensive care unit admission or ventilator use (42%), and fatal cases (22%).

In the management of patients with diabetes mellitus, 265 participants (50%) reported experiencing challenges in controlling blood glucose levels. The primary reasons for these challenges were as follows: corticosteroids administered for COVID-19 pneumonia treatment (64%), inability to attend necessary examinations due to isolation (54%), and the onset of conditions like diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) (38%).

There were as many as 382 participants (72%) who responded that COVID-19 pandemic had negative effects on the management of obesity (Fig. 1).

The major negative effects on the management of obesity due to COVID-19 were as follows: experiencing cases who had obstacles to exercise therapy (95%) and obstacles to dietary therapy (73%) (Table 4).

Similar to diabetes mellitus, many of the participants encountered obese patients with moderate cases of COVID-19 infection (37%), severe cases of COVID-19 infection (26%), and fatal cases (8%).

Dyslipidemia and hyperuricemia

There were 275 participants (52%) who responded that COVID-19 pandemic had negative effects on the management of dyslipidemia (Fig. 1).

The major reasons for negative effects on the management of dyslipidemia due to COVID-19 pandemic were as follows: a shift towards a predominantly home-based lifestyle, leading to an increased risk of lipid abnormalities (84%) and a reluctance to visit medical facilities, resulting in delayed treatment interventions (58%) (Table 4).

In the management of dyslipidemia in patients with COVID-19 infection, 67 participants (13%) reported they had experienced difficulties.

The major reasons included the inability to attend necessary examinations due to isolation (75%) and the inability to prescribe necessary medications (65%).

There were 157 participants (30%) who responded that COVID-19 had negative effects on the management of hyperuricemia (Fig. 1).

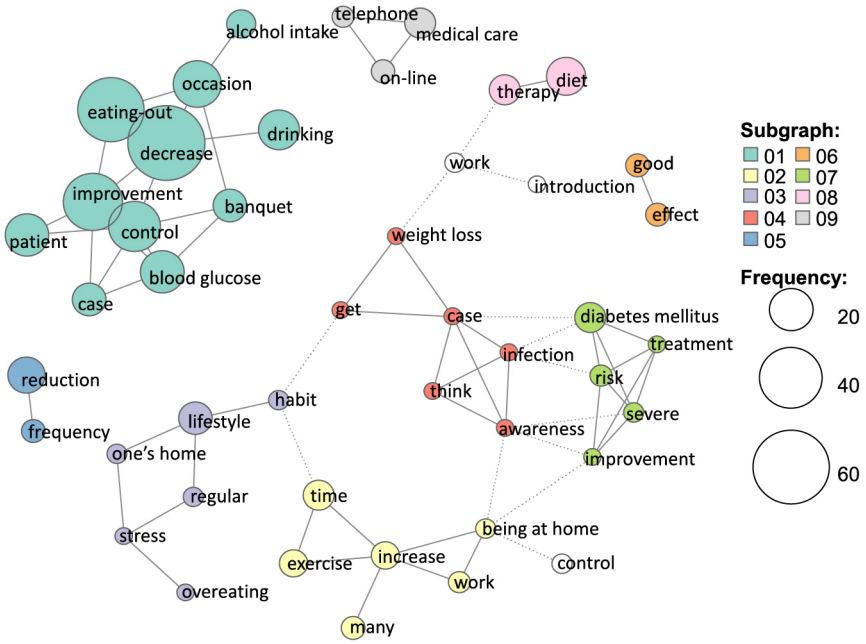
The major reasons for negative effects on the management of hyperuricemia due to COVID-19 pandemic were as follows: a shift towards a predominantly home-based lifestyle, leading to an increased risk of hyperuricemia (75%), a reluctance to visit medical facilities, resulting in delayed treatment interventions (56%), and interruptions of regular medical visits (45%) (Table 4).

In the management of hyperuricemia in patients with COVID-19 infection, 31 endocrinologists (6%) reported they had experienced difficulties.

The major reasons included the inability to attend necessary examinations due to isolation (83%) and the inability to prescribe necessary medications (64%).

Text mining

A text mining analysis was performed for the diabetes area with more than 50 responses regarding the reasons for the positive effects of COVID-19 pandemic on medical practice. Co-occurrence networks analysis is shown in Fig. 2, and a co-occurrence network diagram including the notation of the language of analysis is shown in Supplementary Fig. 3. The largest response category was extracted related to “Lifestyle improvement due to decrease in eating out and meeting at restaurants” (n = 72, 13.6%). Next, responses related to “Lifestyle changes associated with remote working” (n = 10, 1.9%) and “Improvement in understanding of the disease in relation to infection prevention and control of long COVID” (n = 8, 1.5%) were extracted as response groups with relatively broad keywords. Finally, a group of responses related to “Expansion of video and telephone telemedicine” was extracted as a characteristic response group (n = 9, 1.7%).



No	Response	Frequency (*n*, %)
#1	Lifestyle improvement due to decrease in eating out and meeting at restaurants	72, 13.6%
#2	Lifestyle changes associated with remote working	10, 1.9%
#3	Improvement understanding of the disease in relation to infection prevention and control of sequelae of COVID-19	8, 1.5%
#4	Expansion of online and telephone medical services	9, 1.7%

Fig. 2 Positive impact of COVID-19 pandemic on the diabetes mellitus and their relationships from open-ended questions. Results of Text Mining for Open-ended Responses to the Question, "What positive effects have COVID-19 had on your practice?" in the Diabetes Mellitus Domain: Co-occurrence network and frequency.

Discussion

This surveillance of Japan Endocrine Society-certified endocrinologists revealed the significant impact of the COVID-19 pandemic on endocrine and metabolic care in Japan. However, in several disease areas, such as Hashimoto's thyroiditis and osteoporosis, many participants reported no notable impact. It seems to be due to routine care involving fewer tests and interventions. Many practitioners adopted remote consultations, primarily by telephone telemedicine, with a few incorporating video telemedicine into their practices. The effectiveness of remote consultations, established in Western countries [16-18], is considered valuable for ensuring access to medical care during outbreaks of emerging or re-emerging infectious diseases [19]. In Japan, in 2023, a report indicated that telemedicine combined with face-to-face treatment for psychiatric disorders (depression, anxiety, and obsessive-compulsive disorder) was non-inferior to face-to-face treatment in the Short Form Health Study Mental Component Summary (SF-36 MCS) score. These findings support the potential for widespread use of video telemedicine in a variety of medical conditions [20]. In Japan, it is desirable for telemedicine to become a regular option in non-outbreak situations to ensure access to medical care during future infectious disease outbreaks. In terms of disease, one-third of the participants had experiences with endocrine and metabolic disorders after COVID-19 infection or vaccination, especially abnormalities of thyroid, HPA axis, and glucose metabolism. The details of each disease are discussed below.

Hypothalamic-pituitary disorders

Hypothalamic-pituitary disorders were experienced by 20% of participants after COVID-19 or SARS-CoV2 vaccination, respectively, indicating that it is one of the most common endocrine disorders in these conditions. The majority of these conditions were adrenal insufficiency. There are numerous reports of adrenal insufficiency after COVID-19 infection [21-23]. In many cases, the etiology (primary *vs.* secondary to hypothalamic-pituitary dysfunction) was unknown because many cases lack detailed evaluation of the HPA axis. In this study,

secondary was the most common. On the other hand, there were a few responses for primary, and there were also responses such as "adrenal insufficiency" for which the etiology could not be determined, suggesting that primary adrenal insufficiency should also be kept in mind. It is possible that the use of GCs and ritonavir (a potent CYP3A4 inhibitor) for COVID-19 treatment may have had an effect, but since we did not investigate the treatment of the patients in this study, we cannot say for sure that COVID-19 and HPA axis modulation were directly causally related. Further investigation is needed.

Vaccination is a known trigger for adrenal insufficiency [24], and there are some reports of adrenal insufficiency following SARS-CoV2 vaccination [25, 26]. It is unclear whether the risk is higher in the SARS-CoV2 vaccine, but it is noteworthy that about the same number of participants experienced it as those associated with COVID-19. About 40% of participants reported that the COVID-19 pandemic had negative effects on their practice of hypothalamus-pituitary and adrenal diseases, and few reported positive effects. The most common reason for this was related to GC replacement. The issue of GC replacement is discussed below.

It has been reported that concomitant central diabetes insipidus (DI) with hypopituitarism is a risk for mortality in acutely hospitalized patients [27]. In all patients with central DI admitted to the hospital with COVID-19, consultation with an endocrinologist is recommended [28]. In this survey, few participants experienced difficulties in managing DI related to COVID-19. This may suggest that the most important aspect of DI management for COVID-19 patients is to consult an endocrinologist.

With regard to surgical treatment of pituitary tumors, 14.1% of participants experienced a discontinuation or delay in surgery for cases indicated for surgery, and 13.1% of participants reported a decrease in the number of surgical cases. The most common reason for the decrease was limited use of operating rooms. This was thought to be due to the fact that nasal surgery is positioned as a treatment with a high risk of spreading infection [29]. Salmon *et al.* analyzed pituitary surgery outcomes at 2 years before and after COVID-19 from the TriNetX database and reported that the number of surgeries decreased after COVID-19, but the number of perioperative complications remained the same [30]. Endocrinological remission and relapse rates have not been evaluated and await further analysis.

Thyroid diseases

Thyroid diseases were a common area of examination for participants who encountered abnormalities following COVID-19 infection or vaccination. This study identified 228 cases where participants thought that autoimmune thyroid diseases like Graves' disease and subacute thyroiditis either worsened or emerged due to COVID-19 infection or vaccination. While there have been numerous reports of these conditions following COVID-19 infection or vaccination [31-33], it remains unclear if there is a definitive increase in frequency. The high number of reports could be influenced by the widespread prevalence of COVID-19 and high vaccination rates.

Although there were a substantial number of patients with Graves' disease and subacute thyroiditis, this study suggests that the negative impact on medical care due to COVID-19 infection were not as severe compared to other areas in endocrinology. As much as 30% of participants reported difficulties in managing Graves' disease, with the main issue being access to medical care, including continued treatment and medication therapy. Subacute thyroiditis, presenting with fever, is considered to require medical attention in the context of COVID-19 infection, but the struggle with disease management was not significantly high at 3%. Batman *et al.* reported in the Thyroiditis Related to SARS-CoV-2 vaccine and Covid-19 (THYROVAC) study [34] that the course of subacute thyroiditis following COVID-19 infection or vaccination is no different from conventional subacute thyroiditis. This suggests that patients with subacute thyroiditis may be manageable with the usual treatment and observation protocols.

Regarding surgical treatment of thyroid tumors, 25% of participants reported negative effects on benign nodules, while 22% reported negative effects on malignant tumors due to the COVID-19 pandemic. There was no significant difference between benign and malignant tumors. The reasons for these negative effects varied.

Responses in this study indicating that surgical treatment, which was hindered by the COVID-19 pandemic, was more prevalent for malignant tumors compared to benign nodules. On the other hand, 18% of participants reported a decrease in surgeries for benign nodules, while 13% of participants reported a decrease for malignant tumors, indicating a tendency to postpone surgeries more for benign nodules. Generally, thyroid tumors, even if malignant, have a favorable prognosis, and delaying surgery is not perceived as detrimental, especially for benign nodules. A retrospective analysis of data from the National Cancer Database (USA) from 2004 to 2016 reported that prolonged waiting periods for thyroid cancer surgery led to a decrease in 5-year survival rates [34]. However, thyroid cancer surgeries during the COVID-19 pandemic experienced only a short delay (median 62 days, 34–99 days), with little to no impact within that range [35]. In the future, it is desirable to investigate the increase in waiting days for thyroid surgery and its

impact on prognosis in Japan. Another report from the USA indicates a decrease in the number of thyroid surgeries since early 2020, and as of December 2022, inpatient surgery numbers have not yet recovered [36]. This may be attributed not only to restrictions on operating room usage but also potentially affecting diagnoses and long-term surgical numbers. Investigating the impact of delayed diagnoses is also recommended for future study.

Parathyroid diseases and osteoporosis

Among participants who encountered abnormalities following COVID-19 infection or vaccination, very few reported examining parathyroid diseases. Additionally, only 14% of participants reported negative effects on the management of parathyroid disease due to the COVID-19 pandemic. The primary factor for these negative effects was difficulty in diagnosing parathyroid disease, with the second factor being hindered surgical treatment. The most common reason for decreased surgeries was restrictions on operating room usage. Some reports from the USA [35, 36] suggest that among surgeries in the endocrine field, parathyroid diseases were significantly affected by the COVID-19 pandemic. However, in Japan, it seems that participants did not perceive significant impact. This may be attributed to the rarity of parathyroid cancer and the relatively low occurrence of primary hyperparathyroidism with symptomatic hypercalcemia in recent years. Additionally, symptomatic hypercalcemia can be managed with calcimimetics, such as cinacalcet or evocalcet. As mentioned in one report from the USA, the number of surgeries has not yet recovered as of December 2022, similar to thyroid surgeries [36]. This suggests that delayed diagnoses may be impacting the situation, emphasizing the importance of investigating the impact of delayed diagnoses for future study. When focusing on musculoskeletal health, 22% of participants reported negative effects on the management of osteoporosis due to the COVID-19 pandemic. The majority of the reasons were related to issues with medical access, such as difficulties in diagnosis and treatment. Since osteoporosis patients are predominantly elderly, and they largely overlap with the group at higher risk of severe complications from COVID-19 infection, this may have been one of the factors contributing to worsened access to healthcare.

Adrenal diseases and hypertension

About half of the participants reported that COVID-19 had a negative impact on their practice for hypertension. The main reasons for this were attributed to reduced access to medical care, such as delayed diagnosis, delayed initiation of treatment, and difficulties in continuing treatment. Regarding the practice of primary aldosteronism, 22% of the participants indicated that there was a negative impact, mainly due to reduced access to medical care. In the USA, it has been reported that outpatient visits were reduced during a COVID-19 pandemic, mainly due to fear of infection [37], and that blood pressure control worsened in hypertensive patients during the pandemic [38]. On the other hand, some reports indicate that, although the COVID-19 pandemic led to a decrease in visits by hypertensive patients, there was no significant change in blood pressure control [39]. It seems certain that an infectious disease epidemic leads to a decrease in the number of hypertensive patients seen, but whether this leads to a worsening of hypertension may depend on other factors, such as the number of prescription days and the use of telemedicine [40].

As mentioned in the section on hypothalamic-pituitary diseases, adrenal insufficiency is one of the most common endocrine disorders associated with COVID-19. Sixteen percent of the participants indicated that the COVID-19 epidemic increased the frequency of adrenal insufficiency treatment mainly due to the development of adrenal insufficiency caused by COVID-19. There have been case reports of adrenal insufficiency related to acute vascular complications (*e.g.*, bleeding/thrombosis) after COVID-19 [22, 41, 42], but in general, adrenocortical function is reported to be preserved in COVID-19 patients [43]. Therefore, it seems more reasonable to assume that the adrenal insufficiency experienced in COVID-19 is a patient with potentially impaired HPA axis function that is manifested by the burden of COVID-19 infection. In this sense, the issue of steroid coverage during COVID-19 infection in patients with adrenal insufficiency is even more important. Indeed, 16% of the participants faced challenges with steroid coverage. When encountering a physical stress, such as an infection, a "stress dose" of GC beyond the physiologic dose is necessary to avert adrenal crisis. Carosi *et al.* reported that the severity of COVID-19 in patients instructed and compliant with GC escalation during infection did not differ from infected patients without adrenal insufficiency [44]. It is unclear whether the risk of adrenal insufficiency is higher in the SARS-CoV2 vaccine, but in this study, the number of participants who experienced adrenal insufficiency at the time of COVID-19 infection and at the time of vaccination was similar. The dose requirement for GC administration during the peri-COVID-19 vaccination period in patients with adrenal insufficiency is unclear. Bando *et al.* reported that among adrenal insufficiency patients on GC supplementation, only 8.3% required an increase in GC supplementation after vaccination in the first dose and 27.5% in the second dose, and none of the patients who did not receive a GC dose escalation developed adrenal

crisis after vaccination [45]. In this study, more than half of the participants did not explain to their patients about increasing the GC dose in the event of COVID-19 infection, and about a quarter of the participants did not mention increasing the GC dose in the event of an adverse reaction after vaccination. Consensus building with patients regarding emerging viral infections, management of increased GC requirements at the time of vaccination, and supplemental doses is important.

Diabetes mellitus and obesity disease

The percentage of participants who reported that the COVID-19 pandemic had negative effects on their practice was as high as 86% for diabetes mellitus and 72% for obesity disease. The most common reason given for the negative effects was that it interfered with diet and exercise therapy. This is because many diabetic and obese patients were unable to exercise outdoors during the pandemic, and spent more time at home and were prone to snack more due to stress and other factors [46]. Many participants also reported the changes in their hospital environment such as longer intervals between patient's visits, the start of telephone consultations, and the discontinuation of diabetic patient meetings and diabetes classes for the patients. A longitudinal study conducted in Tokyo, comparing the pre-pandemic and pandemic periods, reported that there was a significant increase in delayed consultations and prescriptions during the pandemic period [47]. This result and the reports from other countries [15] support the results of this questionnaire survey. The impact of the change in outpatient care on disease management was not clear in this survey, and further investigation is needed.

On the other hand, only a small number of participants (28%) responded that the COVID-19 pandemic had positive effects. However, the text-mining analysis revealed that many of them responded that the patient's lifestyle improved as they ate out less and socialized less with others, indicating that the restrictions on going out due to the COVID-19 pandemic was beneficial in some aspects in the treatment of diabetic patients. In addition, some respondents indicated that the pandemic has led to expansion of video and telephone telemedicine. Remote consultations were said to be compatible with the treatment of lifestyle-related diseases such as diabetes [16-18], and the use of remote consultations are expected to expand in the future.

Diabetic patients and obese patients are at risk for severe COVID-19, and diabetes and obesity are two of the chronic diseases that are significantly affected in COVID-19 infection [48].

In fact, about half of the participants in the survey had experienced moderate to severe COVID-19 infections in diabetic patients. More than half of the participants had also experienced cases in which the infection made glycemic control difficult. The number of physicians who had experienced severe infections in obese patients was lower than in diabetic patients, but this may be due to the difference in the number of patients attended as obese *versus* the number of patients attended as diabetic, because diabetic patients who are obese are treated only as diabetics and not as obese patients.

There were many diabetic patients who had hyperglycemia associated with corticosteroid administration for COVID-19 pneumonia and who developed hyperglycemic crisis such as DKA and HHS associated with the infection. Various cases of hyperglycemic crisis has also been reported [49, 50], and hyperglycemia without diabetes associated with COVID-19 infection and the development of new diabetes mellitus with the infection are also under discussion [51]. Hyperglycemia is an important prognostic factor in COVID-19 infection and ways to prevent it need to be considered, such as further education for diabetic patients about sick day and the establishment of a hyperglycemia prevention protocol for COVID-19 treatment.

Dyslipidemia and hyperuricemia

It has been suggested that the home-centered lifestyle has had negative effects on the treatment of dyslipidemia and hyperuricemia as well as diabetes and obesity. There is a report that flares were 9 times more frequent during pandemic in gout patients, and also that they had increased urate levels [52]. There is also an interesting review that gout patients are likely to be at an increased risk of poor outcomes after COVID-19 infection due to comorbid cardiometabolic conditions. The effects of chronic hyperuricemia and the hyperinflammatory state induced by gout itself may also play a role. There is a risk of worse prognosis after COVID-19 infection due to coexisting cardiovascular disease, which may be influenced by inflammation associated with chronic hyperuricemia and gout attacks [53]. Reports on dyslipidemia and hyperuricemia and COVID-19 infection are still not many worldwide, and further accumulation of data is required.

Conclusion

This study aimed to elucidate the impact of the ongoing COVID-19 pandemic, which has lasted for over three years, on the diagnosis and treatment of endocrine and metabolic disorders in Japan. To achieve this, a nationwide survey targeting board-certified endocrinologists, conducted by the Japan Endocrine Society, focused on the current situation and challenges in clinical practice.

There is no precedent for such a large-scale and detailed nationwide survey specifically targeting board-certified endocrinologists with a focus on challenges in the diagnosis and treatment of endocrine and metabolic disorders when facing unpredictable emerging infectious diseases. The scientific extraction of these problems is expected to provide valuable insights for establishing rational and scientifically responsive measures for potential future outbreaks of emerging and re-emerging infectious diseases, contributing to the development of a more robust healthcare system.

The endocrinologists who experienced cases with some form of endocrine and metabolic disorders following the COVID-19 infection or vaccination exceeded 30%. Particularly in thyroid diseases, glucose metabolism disorders/diabetes mellitus, and hypothalamic-pituitary disorders, a significantly higher tendency was observed compared to other endocrine and metabolic disorders, marking an important new finding.

Furthermore, the endocrine and metabolic disorders with particularly high rates of severe cases or fatalities due to COVID-19 infection were diabetes and obesity, which were compatible with previous reports both domestically and internationally.

Through this study, several underlying challenges in the routine diagnosis and treatment of endocrine and metabolic disorders have come to light. The effective combination of remote consultations with in-person visits to optimize the frequency of examinations and check-ups has the potential to bring significant benefits not only during infectious disease outbreaks but also in non-emergency times, especially in the management of endocrine and metabolic disorders that often require ongoing care.

This study has several limitations of note. This study specifically targets specialists in endocrine and metabolic disorders and may not directly apply to general medical practice. This study is a survey targeting only the subjective opinions of physicians, and there has been no confirmation of consistency with objective indicators or evaluations from sources other than physicians. Although a “complete survey” was initially assumed for the survey procedure, the response rate from endocrinologists at hospitals was higher than the response rate from endocrinologists at clinics, potentially introducing a sample bias. Based on the sampling surveillance on the facilities of the target population, it appears that there were relatively fewer respondents from clinics compared to other facilities. There might be biases, such as specialists who participated in this study being from facilities that accepted patients hospitalized due to COVID-19 and had more opportunities to treat patients with endocrine and metabolic disorders related to COVID-19. In addition, there were regional differences in response rates. Compared to the facility location of the entire target population, the response rate was lower in the Kanto region and higher in the Chubu and Kyushu regions. Regarding multiple responses from physicians within the same facility, no weighted correction has been made to account for facility-dependent factors. Additionally, there is a possibility that factors such as the age, gender, and geographic region of the respondents may not fully represent the overall subjects due to relying on voluntary responses. However, considering that there may be several more waves of COVID-19 before the healthcare system can fully return to normal, the insights obtained from this survey are helpful in contributing to ensuring appropriate healthcare provision for patients with endocrine and metabolic disorders during new waves of COVID-19, and ultimately in conditions where medical access may be limited due to future outbreaks of emerging or re-emerging infectious diseases.

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Author Disclosure Statement

The authors state that they have no conflicts of interest related to this study.

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Author Contribution

H.M. and H.A. designed the study. T.U. performed administrative tasks including an ethical review. All authors participated in compiling and revising the questionnaire. K.M., S.K., R.S., and H.Y. analyzed the data and wrote the initial draft, and H.M., N.S.-A., H.A., and M.F. edited the manuscript. All authors reviewed and approved the final draft of the manuscript.

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