Patient Preference and Adherence

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ORIGINAL RESEARCH

Growth Hormone Injection Log Analysis with Electronic Injection Device for Qualifying Adherence to Low-Irritant Formulation and Exploring Influential Factors on Adherence

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Introduction: Although the treatment success of long-term growth hormone therapy (GHT) is dependent on maintaining patients' adherence to treatment, marked variations in adherence levels among children with GHT (eg, 7–71% nonadherence) have been reported. Barriers to or promoters of GHT adherence have been discussed and investigated, and digital health technologies, such as electronic GH injection devices, may have the potential to assess adherence to GHT more accurately. Thus, we conducted a multicenter, retrospective cohort study using GH injection log analysis of an electronic GH device, GROWJECTOR®L, to qualify adherence and explore the factors influencing adherence.

Methods: This study enrolled 41 patients (median[range] age, 5.8[3.0 ~ 17.0] years) with short stature from nine Japanese medical institutions. The injection log data (12–48 weeks) were read by smartphones and collected into the data center through a cloud server.

Results: Although cumulative adherence rates remained higher than 95% throughout the observation period, five (12.2%) patients had low adherence (<85%). Subsequently, subgroup and logistic regression analyses for exploring factors affecting adherence revealed that self-selection of GH device and irregular injection schedule (ie, frequent injections after midnight) significantly affected adherence rate (p=0.034 and 0.048, respectively). In addition, higher rates of irregular injections significantly affected low adherence (median[range], 11.26[0.79 ~ 30.50]% vs 0.26[0.00 ~ 33.33]%, p = 0.029).

Discussion: Our study indicated that injection log analysis using an electronic GH device could detect irregular injection schedules due to a night owl or disturbance in lifetime rhythm affecting low adherence and had significant potential to encourage collaborative monitoring of adherence with healthcare providers and patients themselves/caregivers, along with growing autonomy and shared decision-making. Our study suggests the significance of narrative and personal approaches to adherence of patients with GHT and the usefulness of digital devices for such an approach and for removing various barriers to patient autonomy, leading to improvement and maintenance of adherence.

Keywords: GH therapy, digital health technology, shared decision- making, patient autonomy

Introduction

The treatment success of several chronic conditions, including those requiring long-term growth hormone therapy (GHT), is dependent on maintaining and improving patients' adherence to treatment. Since the development and widespread clinical use of

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recombinant human growth hormone (rhGH, somatropin) in 1985,[1] GHT has been applied to a range of growth disorders, including GH deficiency (GHD) and non-GH-deficient disorders, such as Turner syndrome (TS), short stature related to small for gestational age (SGA), Prader–Willi syndrome, chronic renal insufficiency, achondroplasia, and Noonan syndrome. Several studies have reported marked variations in adherence levels among children receiving rhGH treatment (eg, 7–71% of the prevalence of nonadherence in the systematic review conducted by Graham et al).[2] Barriers to or promoters of GHT adherence in pediatric patients have been discussed and investigated.[3] In previous studies, different methods, including self-report questionnaires to patients and/or caregivers and issued, renewed, or redeemed rhGH prescriptions/vials, have been used to measure medication adherence.[2] A more objective, accurate, and quantitative method of assessing adherence remains an issue.

Digital health technologies have become an increasingly essential part of humans' daily lives; consequently, they have a high potential to support patients and caregivers in their health management.[4] There are several GH delivery devices, including syringes, pens, and auto-injector devices, such as the easypod® auto injector, which transmits data to a web-based platform that allows monitoring adherence and integrating data for big data analysis. The easypod connect observational study (ECOS) produces accurate, real-time adherence data in a large population of GH-treated children in 24 countries over 5 years of follow-up and represents a potential of electronic GH devices for more accurately assessing adherence to GHT.[5] Although big data analysis in the ECOS indicated several factors associated with worse adherence, it has yet to be reached to resolve non-adherence fundamentally.

Another recently launched electronic GH device, GROWJECTOR® L (GTL; PHC Holdings Corporation, Tokyo, Japan) for the subcutaneous administration of the rhGH, GROWJECT® (6 and 12 mg; JCR Pharmaceuticals Co., Ltd., Ashiya, Hyogo, Japan), was launched in January 2017 for the Japanese market only. GTL enables a series of automatic injects and stores injection logs, resulting in precise analysis of medication adherence data. A multicenter, prospective cohort study using GTL indicated that GH injection log analysis was useful for assessing adherence rates and individual injection timing, which could affect adherence.[6] Therefore, we conducted a multicenter, retrospective cohort study using GH injection log analysis of GTL to qualify adherence to the newly formulated rhGH, which was launched in April 2020,[7] and to explore factors influencing adherence.

Materials and Methods

Subjects

This multicenter, retrospective cohort study was conducted between April 2020 and May 2021 at nine Japanese medical institutions. Patients treated with the GTL for short stature associated with GHD, TS, or SGA with open epiphyseal plates were screened for eligibility by the investigators at each institution. Study participants with written informed consent from both parents or caregivers of the patients, along with informed assent if applicable, were registered at the contracted central data center (Kondo P.P. Inc.) after anonymization at each center. The inclusion criteria were as follows: age ≥3 years; start of treatment with the GTL; and any of the following conditions: (1) patients within 3 years of starting GH treatment with the prior formulation of rhGH in April 2020 (prior formulation group) and (2) patients who started GH treatment with the new formulation of GTL which was bioequivalent to the prior formulation and associated with less injection site pain[7] between April 20, 2020, and March 31, 2021 (new formulation group) (Figure 1). All patients and parents or caregivers received education and training of the GH device by pediatric endocrinologists or pediatric nurses using uniformed explanatory materials. The exclusion criteria were as follows: contraindications to GHT (eg, diabetes, malignancy, and [possible] pregnancy) and physician discretion. Considering the explorative nature of this study, the target sample size was determined based on recruitment during an 11-month period in the nine study centers rather than statistics. Therefore, approximately 40 patients were included in this study.

Study Design

The GTL device can store almost 400 injection log data, which almost correspond to a treatment record for 1 year. After obtaining consent from the patients and caregivers, injection log data were read by a smartphone via near-field communication and collected into the data center through a cloud server. The observation periods were over 12 weeks, indicating the period during which injection data could be retrieved until the day of log data collection. The

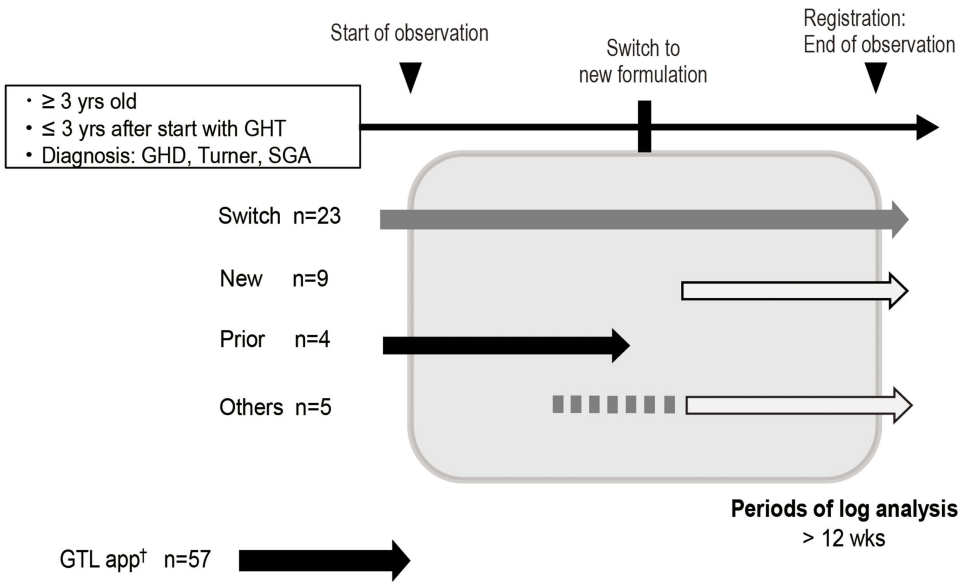

Figure 1 Study design.
Notes: †The previous study[2] using the prior formulation of rhGH for treatment naive GHD patients.

physicians registered the data of patients and their treatment as follows: date of birth, sex, diagnosis, date of starting GHT, height at the time of enrollment, person who performed the injection, body site of injection, number of doses per week, type of needle, use of treatment support application, whether or not the treatment device is self-selected, and date of switching to the new formulation for cases where treatment was started with the prior formulation and switched to the new formulation (if possible). No interventions were provided during the study period. GHT was administered to the patients as part of routine daily clinical practice.

The primary endpoint was the medication adherence rate, which was defined as the total number of injections received divided by the total number of injections planned over each observation period. The secondary endpoints were factors associated with low adherence, defined as an adherence rate <85% (ie, almost more than one miss of injection per week).[8–13]

Statistical Analyses

Continuous variables are expressed as medians (ranges), whereas categorical variables are expressed as numbers (percentages). After stratification based on the dosing pattern of rhGH formulations and background characteristics, adherence rates of the patients were compared between groups using the Kruskal–Wallis test and Mann–Whitney *U*-test or Wilcoxon signed-rank test, respectively. Factors associated with nonadherence were explored using a logistic regression model, and odds ratios and 95% confidence intervals were estimated. Considering the sparseness of the data, Firth's bias correction method was used for the logistic regression analysis. In addition, post-hoc exploratory analyses were performed according to clinical interest, such as the average daily injection time during the observation period. No adjustments were made to the multiplicity of the statistical tests, considering the exploratory nature of this study. Statistical significance was set at $p < 0.05$. All statistical tests were performed using SPSS version 28 (IBM Corporation, Armonk, NY, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki (Fortaleza revision, 2013) and the ethical guidelines for medical and health research involving human subjects provided by the Japanese Ministry of Health, Labour and Welfare (revised 2017). The study protocol was approved by the Ethics Committee of the Tokyo Medical and Dental University and the ethics review board of each study site. All the subjects provided written informed consent. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000041833).

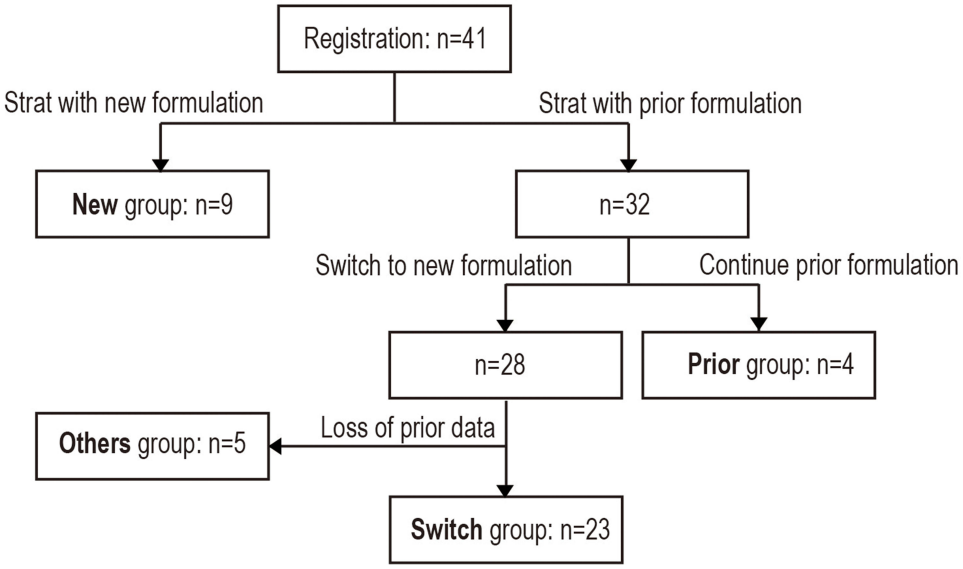

Figure 2 Flow diagram of participants.

Results

Patient Disposition and Baseline Characteristics

This study enrolled 41 (22 boys) patients with short stature, including 20 with GHD (48.8%), three with TS (7.3%), and 18 with SGA (43.9%) from nine Japanese medical institutions. A patient flow diagram is shown in Figure 2. Nine patients started the new rhGH formulation (New group). Of the other 32 patients, four were newly started with and continued for more than 12 weeks the prior formulation (Prior group), 23 were switched to the new formulation (Switch group), and five were switched formulations but lost log data when using the prior formulation (Others group). The baseline characteristics of the 41 patients are summarized in Table 1.

Table 1 Patient Data

Numbers of Patients	41	(22 boys)
GHD	20	(13 boys)
Turner	3	
SGA	18	(9 boys)
At start of GHT		
Age (yrs)	5.1	[2.4–14.2]
Formulation	Prior formulation: 32	New formulation: 9
Patient choice	25	(61%)
Frequency of administration	Six times/wk: 21	Every day: 20 (49%)
Needle thickness	32 gauge: 11	34 gauge: 30 (73%)
At start of observation		
Age (yrs)	5.8	[3.0–17.0]
Duration of treatment (days)	202	[0–1092]
At registration (end of observation)		
Age (yrs)	6.8	[3.9–17.5]
Height SDS	−2.04	[−3.77~0.08]
Duration of observation (days)	348	[87–777]
Person who administers injections	Patient his/herself	5
	Mother	33 (81%)
	Father	11
	Grandmother	1

Notes: Patient choice, choice of GH injection devices by patients and caregivers.

The median (range) age of the patients at the start of observation was 5.8 (3.0 ~ 17.0) years, and the median period from the start of GT therapy to the start of observation was 202 (0 ~ 1092) days. Twenty-five (61.0%) patients self-selected their treatment device. At registration (ie, end of observation), the median age, height standard deviation (SD) score, and observation period were 6.8 (3.9 ~ 17.5) years, −2.04 (−3.77 ~ 0.08), and 375 (87 ~ 777), respectively. In 80.5% of the patients, the mothers executed injections, and only 12.2% of patients self-injected rhGH.

Effect of Switching to the New Formulation on Adherence Rates

In 23 patients in the Switch group, the median adherence rates before and after switching were 98.1% and 98.6%, respectively, which were not significantly different (p = 0.586, Figure 3). In addition, the median adherence rates in the Prior and New groups were 97.4% (97.2–100) and 98.6% (83.3–100), respectively, which were not significantly different (p = 0.753). These were not significantly different from the median adherence rates at 12 weeks of observation of patients in the prior study (97.6% [63.1–100]),[6] who were started with the prior rhGH formulation (p = 0.635 and 0.542, respectively, on the Mann–Whitney *U*-test). These data indicate that switching the rhGH formulation does not reduce adherence.

Exploring Influential Factors on Low Adherence Through Injection Log Analysis

The cumulative adherence rates during the observation period calculated at 12, 24, and 48 weeks are shown in Figure 4. Although the cumulative adherence rates remained high throughout the observation period, a few patients had low

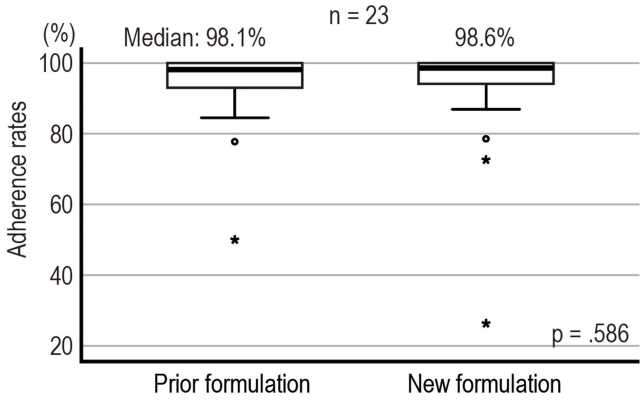

Figure 3 Comparison of adherence rate between the prior and new formulations.
Notes: The circles indicate mild outliers; observations that fall 1.5 to 3 times the interquartile range less than 1st quartile. The asterisk indicates an extreme outlier; observations that fall over 3 times the interquartile range less than 1st quartile.

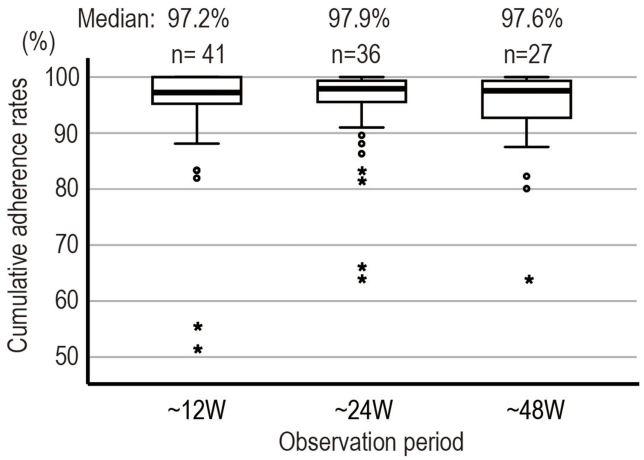

Figure 4 Time course change in the cumulative adherence rate from 12 to 48 weeks observations.
Notes: The circles indicate mild outliers; observations that fall 1.5 to 3 times the interquartile range less than 1st quartile. The asterisks indicate an extreme outlier; observations that fall over 3 times the interquartile range less than 1st quartile.

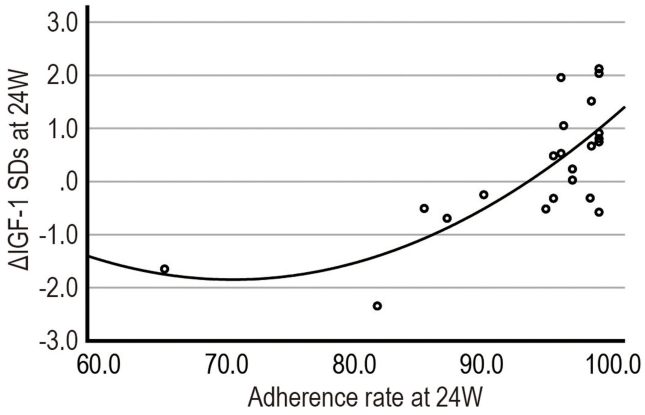

Figure 5 Correlation between adherence rate and ΔIGF-1 SDs at 24 weeks observations.

adherence (<85%). In addition, changes in insulin-like growth factor-1 (IGF-1) SDs at 24 weeks were significantly correlated with adherence rates (correlation coefficient = 0.676, p = 0.001) (Figure 5).

The characteristics of the five patients with low adherence identified by the injection log data analysis are shown in Table 2. Two of the three patients with GHD showed a relatively low adherence rate of <60% (ie, almost more than three times the miss of injection per week), for which a more proactive intervention may be required. One of the two patients who were SGA showed low adherence shortly after starting GH therapy, which may indicate an insufficient initial introduction. Detailed analyses of injection logs revealed that four of the five (80%) patients with low adherence often had irregular injection schedules, including injection after midnight and multiple injections simultaneously.

To explore factors affecting adherence, subgroup analyses based on adherence rates during the 24 weeks of observation were performed (Table 3). Diagnosis, sex, age, treatment period, height SD score, number of doses per week, type of needle, and person who performed the injection did not affect adherence, whereas self-selection of the GH device and irregular injections significantly affected adherence rates (p = 0.034). Furthermore, a logistic regression analysis of influential factors on low adherence (Figure 6) revealed two insights. First, a low height SD score at registration (ie, at the end of the observation period) affected low adherence (odds ratio, 13.0; p = 0.031), indicating that low adherence may lead to lower gain in height. Second, irregular injections (ie, frequent injections after midnight [> once a month]) affected low adherence (odds ratio, 8.4; p = 0.048), indicating that a derailed injection schedule may be a sign or trigger of low adherence. Rates of irregular injections after midnight to all injections in the patients varied from 0% to 33.3%, and higher rates of irregular injections significantly affected low adherence (median [range], 11.26 [0.79 ~ 30.50] % vs 0.26 [0.00 ~ 33.33] %, odds ratio, 2.5; p = 0.029).

Table 2 Characteristics of Patients with Low Adherence

Age (Years)	Sex	Diagnosis	Treatment Duration (Days)	Person Who Administers Injections	Patient Choice	Adherence Rate (%)			Irregular Injection	
						12W	24W	48W	Frequent†	Rate (%)
9.8	M	GHD	241	Caregivers	–	55.6	66.0	64.2	+	3.6
9.7	F	GHD	421	Caregivers	–	83.3	86.3	80.1	–	0.3
13.5	M	GHD	1070	Self	+	51.2	64.3	–	+	19.0
5.0	F	SGA	0	Caregivers	–	83.3	81.3	–	–	0.8
4.5	M	SGA	202	Caregivers	+	81.9	82.6	82.3	+	30.5

Notes: †Frequent GH injections after midnight over once a month. Patient choice, choice of GH injection devices by patients and caregivers.
Abbreviations: GHD, growth hormone deficiency; SGA, small for gestational age.

Table 3 Subgroup Analyses Based on Adherence Rate During 24 Weeks Observation

Item	Groups	P value
Diagnosis	GHD, Turner, SGA	0.492
Sex	Male, Female	0.400
Age at registration	<10 years old, ≧10 years old	0.290
Duration of treatment	~24W, 24~48W, 48~96W, 96W~	0.867
Height SDS at registration	<median, ≧median	0.399
Frequency of administration	Six times/week, Seven times/week	0.482
Needle thickness	32 gauge, 34 gauge	0.709
Injection by patient his/herself	Presence, Absence	0.890
Patient choice	Presence, Absence	0.034*

Notes: Patient choice, choice of GH injection devices by patients and caregivers. *p<0.05.

Discussion

Although the wider adaptation and implementation of digital health is still a major challenge, significant effort has been put into the development of digital tools for health interventions to treat chronic conditions, including pediatric endocrine diseases. Digital health technologies can provide data-driven self-management tools to improve patients' autonomy and adherence to treatment. Closed-loop insulin delivery systems and smart insulin pens for type 1 diabetes mellitus are good examples. New technologies for GH devices can more accurately monitor and quantify patients' adherence to GH therapy, leading to the development of big data analytics for the improvement of patient support and personalized medicine to advance patient autonomy.[14] By way of an example for big data analytics, the ECOS since 2007 has included real-world adherence data of over 20,000 patients from 38 countries,[15,16] indicating an increasing tendency of high adherence population rates (68–88%) and regional differences (88% in North America, 86% in Europe, and 68–73% in Asian countries).[4,16] Based on integrated patient-generated data, a continuous feedback loop with hypothesis verification configured by patients, caregivers, data scientists, and healthcare providers has the potential to improve disease management and patient support and evolve digital health ecosystems over time.[4,14] As with the previous Japanese study,[6] the high adherence population rates in this study (approximately 90%) are higher than the ECOS data in Asia and may reflect the current status in Japan. In addition, to the best of our knowledge, this study is the first attempt to evaluate the effects of formulation changes on adherence using an electronic device in clinical practice.

Another benefit of digital health technology in GH devices is the promotion of personalized medicine and patient support. Several researchers have been looking into the several factors that affect or drive medication adherence,[2,3,14,17,18] and these often highlight regional or individual differences in cultural or economic backgrounds, perceived significance, and literacy levels. Injection log analysis can reveal the presence or absence of injection and the

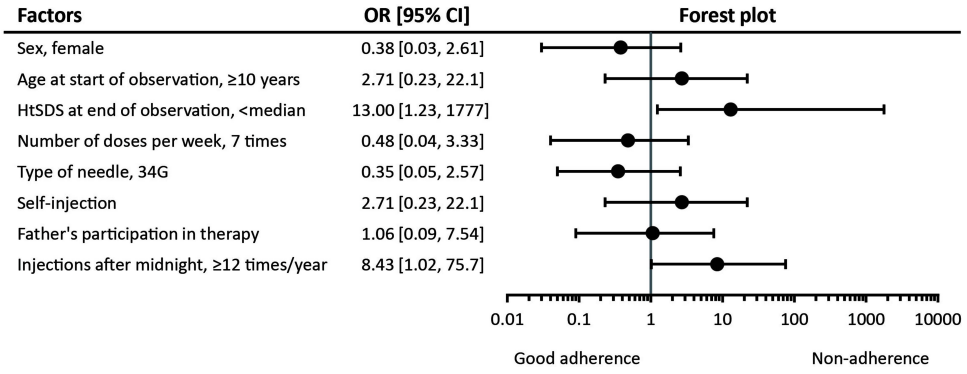

Figure 6 Forest plots for the logistic regression analysis of influential factors on low adherence.
Abbreviations: OR, odds ratio; CI, confidence interval.

characteristics of patients with low adherence and issues to be addressed individually. A previous study suggested the possibility of delayed injection time being relevant to low adherence.[6] Our study indicated that irregular injection schedules, including frequent injections overnight or carried forward due to a night owl or disturbance in lifetime rhythm, could affect low adherence. The early detection of signs affecting low adherence could lead to earlier interventions with lifetime guidance and construct individualized patient support.

Various discussions and approaches on factors affecting adherence have been made.[2,3,18] These approaches can be divided into two phases: initial introduction and maintenance. GHT can improve patient growth and quality of life 1 year after initiation;[19] however, the low adherence population gradually increases until 3–5 years after initiation.[12] Although low adherence from the start can be prevented by improvement of the initial introduction, interventions for maintenance of high adherence need to be determined, and there is no clear solution for the recovery of lowered adherence. Certainly, patients with low adherence in this study had lower ΔIGF-1 and height gains, indicating a reduced therapeutic effect.

A change in healthcare practices from a medical paternalistic to a more patient-autonomous approach to health care have placed enormous importance on a shared decision-making (SDM) process by which patients are actively encouraged to participate in their own healthcare decisions. Growing evidence has suggested that SDM may promote patient adherence to GHT.[18] For example, the choice of GH injection devices by patients and caregivers, the so-called "patient choice", promotes family member participation and retains adherence to GHT, resulting in improved therapeutic effects.[20] SDM encourages patients and caregivers to take an active and informed role in their therapy and a greater "ownership" and satisfaction (ie, self-efficacy with their treatment). Opportunities for SDM during a patient's treatment journey include the decision to begin treatment, patient choice, and goal setting and if and how to self-monitor adherence and when to review treatment plans following the transition to adolescent growth progress.[18] Injection log analysis indicated that digital health technology had significant potential to encourage collaborative monitoring of adherence to GHT by healthcare providers and patients themselves/caregivers. In addition, in the transition stage from pediatric to adult health care during a patient's treatment journey, gradually increasing patient responsibility and education will be best supported with SDM and encourage a collaborative effort between pediatric and adult endocrinologists, patients, and their families. Self-injected GH and self-management of GHT by child/adolescent patients may be the assumption of a double-edged sword as a promoter of patient autonomy[3,10] or a risk of low adherence.[6] Objective evaluation of GH injections by log analyses can highlight a fundamental problem with self-injected GH and provide collaboration between healthcare providers and patients themselves with growing autonomy.

A recent hot topic in GHT has been the social implementation of long-acting GH analogs (LAGHs) for children with GHD.[21] Several studies in the developing states and clinical trials demonstrated short-term safety and efficacy of LAGH equivalent to daily injection of GH,[22–25] and LAGHs seem to be attractive as it may theoretically offer increased patient acceptance, tolerability, and therapeutic flexibility by decreasing injection frequency. Certainly, a questionnaire study of patients with GHD and their caregivers in Japan revealed that the injection schedule was the most important factor for both patients and caregivers. Thus, a once-weekly injection schedule of LAGT was preferred over a daily injection schedule.[26] However, several potential pitfalls, including long-term safety, durability of efficacy, methodology of dose adjustments, and cost-effectiveness, have been discussed.[21–23] In addition, the effect of LAGHs on patients with low adherence should be paid attention, because one miss of injection can lead to a larger loss in weekly or biweekly injections than in daily injections. Because our study revealed the importance of punctual injections at a fixed time for maintaining adherence, therapeutic flexibility featured by LAGHs may promote disruption of the injection schedule of patients with low adherence, resulting in worsened long-term adherence. Therefore, a multifaceted assessment of the long-term efficacy of LAGHs, especially on adherence, based on more objective, accurate, and quantitative methods of monitoring adherence (eg, using digital devices) may be required.

In summary, our study revealed two major benefits of GH injection log analysis of the electronic GH device as below: (1) a potential of electronic GH devices for more accurately assessing effects of formulation changes on adherence to GHT and (2) a potential of injection log analysis for revealing hitherto unnoticed factors associated with adherence and promoting personalized patient support. Though our study had two limitations relating to not randomized sampling and small sample size and a potential of injection log analysis had been already discussed in the ECOS, our findings may add confirmatory evidence that injection log analysis could promote personal and narrative approach and multifaceted assessment on adherence of patients and caregivers to GHT.

Conclusion

Digital health technology with technical innovation cannot solve all problems and issues concerning GHT and adherence and is nothing more than a tool. Digital technology is useful for the integration and personalized application of big data and should be utilized to develop new treatment strategies for GHT. Our study suggests the significance of narrative and personal approaches to the adherence of patients and caregivers to GHT and the usefulness of digital devices for such an approach. Further accumulation of analysis and evaluation from multifaceted viewpoints of adherence to GHT and more extensive and individualized studies for identifying problems and issues inherent in each patient with GHT are required. Next steps of our and these studies will be exploring more effective approach and personalized support for improvement of adherence based on feedback of patients. Digital health technology can contribute to these processes and remove various barriers to patient autonomy, leading to the improvement and maintenance of adherence.

Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available due to patient's consent but are available from the corresponding author on reasonable request.

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Disclosure

Dr Keisuke Nagasaki reports lecture fees from JCR Pharmaceuticals Co., Ltd., outside the submitted work. The authors report no other conflicts of interest in this work.

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