Adherence, Attitudes and Beliefs of Growth Hormone Deficient Patients – A Questionnaire-based Cohort Study

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ABSTRACT

Introduction GHD is a chronic and systemic disease requiring daily replacement of growth hormone (GHRT). Adherence and attitudes of adult GHD patients are not well known. We sought to assess patients' knowledge of growth hormone deficiency (GHD) in association with treatment adherence and attitudes regarding available and upcoming treatment options.

Methods We performed a cross-sectional survey with a custom-made questionnaire at a single centre assessing data on demographics, knowledge of GHD, adherence and attitudes towards GHRT.

Results Of 106 eligible patients actively followed for GHD 70 returned the completed survey (return-rate 66 %, 34 m/36 f; age 56 ± 14 years). 46 patients were actively treated, but almost one third (n = 24) refused GHRT. 12 patients had participated in clinical trials with LAGH (long-acting growth hormone). Overall, patients with GHRT showed good adherence. Patients refusing GHRT mostly feared side effects and/or had a lack of information/perceived effect. Disease knowledge and level of education were higher in treated than untreated patients (p = 0.023/0.017). Only 36 % of respondents would initiate treatment with LAGH. Patients with prior LAGH experience and patients with childhood-onset GHD were more likely to adopt LAGH (p = 0.048/0.031).

Discussion Most often, misinformation causes patients to refuse GHRT. Possibly the understanding of their condition and consequences of non-treatment is limited. To improve adherence more focused educational and behavioural strategies may be needed. Willingness to begin a therapy with LAGH was lower than expected (36 %). The reasons for reluctance against LAGH need to be elucidated.

Introduction

Growth hormone deficiency (GHD) is a chronic, etiologically diverse and multi-faceted disease. It leads to abnormal body composition (decreased lean body mass and increased fat mass), osteoporosis, altered lipid and glucose metabolism, as well as reduced quality of life (QoL) and is associated with an increased incidence of cardio-vascular events and increased mortality [1–5]. Treatment consists in replacement with recombinant human growth hormone. Currently, available formulations stipulate daily administration via subcutaneous (s.c.) injections. Growth hormone replacement therapy (GHRT) has proven to be safe and effective [6].

However, symptoms develop gradually and the treatment effect is not immediately noticed by patients due to the lack of acute symptoms, whereas the discomfort of daily injections is a tangible inconvenience. Thus, adherence of GH replacement therapy is an issue that has been explored, particularly in the setting of childhood-onset GHD where low adherence was consistently observed [7–14]. Adherence in adult GHD patients is especially affected by

dissatisfaction with the perceived therapy results and a bad clinician-patient relationship [15]. A significant reduction of adherence and persistence within the first four years of treatment has been described [16]. There have been a number of attempts to improve treatment adherence by utilizing different non-daily dosing regimens including every other-day [17] and 3 times weekly dosing [18–20]. Clinical outcomes were similar, but the effect on adherence remained unclear as some studies showed a better adherence while others did not [21]. Several long-acting rhGH preparations are currently under clinical investigation and thought to potentially improve adherence [22].

Investigations of adherence in patients with adult growth hormone deficiency (AGHD) are scarce [23]. We sought to determine patients' knowledge of the disease and treatment, as well as attitudes towards current treatment options versus newly developed LAGH in patients through a questionnaire-based approach, especially by comparing perception of patients receiving replacement therapy with patients who refuse it. Further objectives were to assess potential factors that influence adherence and persistence.

Methods

Design of the questionnaire

A systematic literature research did not reveal any validated questionnaire eligible for our specific approach. Based on pre-existing adherence questionnaires and published data on specific advantages and disadvantages of their items [24, 25] we created a tailored questionnaire covering the domains of medication taking behaviour, barriers to adherence and beliefs associated with medication adherence. Notably, we adopted most adherence-related items from the Medication Adherence Questionnaire [26], the Hill-Bone Adherence Scale [27] and the Medication Adherence Rating Scale [28] and modified them to fit the context of GH treatment. In particular, we asked patients not currently undergoing GHRT treatment about their reasons for treatment discontinuation. The questionnaire also included a section capturing the knowledge domain concerning GHD by asking the patients to write down symptoms and effects on health of GHD in a short-answer format. The questionnaire also assessed attitudes regarding long-acting GH formulations and requested demographic data including sex, age and level of education. The latter was operationalised by the highest degree of general education following the recommendations of the German statistical federal office. The questionnaire was sent by mail with a prepaid return envelope enclosed, which allowed the patients to remain completely anonymous and not assume any costs for participation. All questions and their possible answers are presented as supplementary material (▶ **Table 1S**).

Questionnaire evaluation

Non-adherence score

The questionnaire included six questions pertaining to adherence. A score ranging from 0 to 18 was computed for every respondent. Four questions were coded with a 5-point Likert scale ranging from "never" (= 0 points) to "more than 3 times per week" (= 4 points): "How often do you forget your growth hormone injections?", "Do you skip injections when feeling healthy and having the feeling that your symptoms are well controlled?", "Do you sometimes skip injections when you're sick?", and "Have you ever injected less than recommended or nothing at all because of feeling worse after injection?" A fifth 5-point Likert scale question ("How often do you forget your medication when traveling or spending the night elsewhere?") was accounted for by dividing the points by 4 to factor in the non-routine role of travel in most people's lives. The last question contained binary information and was awarded one point if disagreed ("Have you injected growth hormone every single day in the past 7 days?"). The score result was then correlated with non-adherence and treated as ordinal data.

GHD knowledge score

The free-text statements from patients about the effects of GHD on health were grouped into different symptom categories. These categories are listed below with exemplary answers as given by patients:

- Physical performance: fatigue, rapid exhaustion ("one is not fit", "one performs worse in sport").
- Metabolism: altered lipid metabolism, altered glucose metabolism ("disturbed metabolism", "diabetes").
- Body composition: reduced muscle mass, increased fat mass, increased abdominal fat mass ("one becomes fat", "one loses muscles").
- Cardiovascular risk factor ("risk for heart diseases").
- Bone mineral density ("osteoporosis").
- QoL and psychological disturbances ("depression", "bad mood", "less well-being").
- Increased mortality ("reduced life expectancy").

A score for knowledge of GHD was calculated by counting the number of different symptom categories mentioned by each patient, regardless of the number of symptoms stated in each category. Hence, a score result of 0 indicates the patient was not able to make any correct statement about the effects of GHD, while a result of three indicates the patient mentioned symptoms belonging to three different categories. The result was treated as ordinal data.

Study population

The questionnaire was distributed amongst 106 adult patients with GHD who attended our Endocrinology Outpatient Clinic at least once since 2000, and who participate in the observational study of the Network of Excellence for Neuroendocrine Tumours Munich (NeoExNET). The local ethics committee granted ethical approval. All study procedures were performed in accordance with the Declaration of Helsinki and all patients gave informed consent. 70 patients completed the questionnaire correctly and returned it (response rate: 66 %). The study population was well balanced in regard to sex distribution (49 % female, 51 % male), onset type (61 % adult-onset, 33 % childhood-onset, 6 % not disclosed) and level of education (data not shown), cf. ▶ **Table 1** for an overview of the study population. Mean age of patients with childhood-onset GHD was 48.7 ± 12.9 years and 60.5 ± 12.1 years in AoGHD patients.

Statistics

Statistical analysis was performed using IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA). Correlations were calculated using Kendall's tau b (ordinal – ordinal), Mann-Whitney U test (nominal –

▶ **Table 1** Demographic data of surveyed patients.

	patients with GHRT	patients without GHRT	all patients
n (% of total)	46 (66 %)	24 (34 %)	70
male/female patients (%)	24: 22 (52 %: 48 %)	10: 14 (42 %: 58 %)	34: 36 (49 %: 51 %)
age (mean ± SD)	57.1 ± 12.7	55.4 ± 15.1	55.9 ± 13.5
childhood: adult onset (%)	15: 31 (32 %: 68 %)	9: 15 (37 %: 63 %)	24: 46 (35 %: 65 %)
Adherence, attitudes and beliefs of growth hormone deficient patients – A questionnaire-based cohort study.			

ordinal) and chi-square test/Fisher's exact test (nominal – nominal). For all calculations concerning adherence only patients under GHRT were considered. P values ≤ 0.05 were considered significant.

Results

Adherence and burden of therapy

76 % of the patients receiving GHRT reported forgetting a GH injection "never" (41 %) or at the most "less than once per month" (35 %), implying good adherence in our study group. On the other hand, 18 % skipped injections occasionally ("less than once per week") and 6 % reported skipping injections several times weekly. None stated forgetting injections more than 3 times per week. 96 % reported they "never" (80 %) or "seldomly" (16 %) skipped an injection because of feeling healthy or the lack of disease symptoms. 98 % of the patients reported to "never" (76 %) or "seldomly" (22 %) skip a dose when ill. Furthermore, patients did not skip doses because of feeling worse after injection ("never" 94 %, "seldomly" 6 %). Accordingly, the mean non-adherence score was very low (2.0 ± 2.5 points; range: 0–11) with a median of 1 out of 18 possible points.

All patients except for one injected GH in the evening, as recommended. Only 10 % reported they felt burdened and 27 % admitted to "sometimes" feeling burdened by GH therapy. In addition, several patients added a handwritten comment reporting they felt burdened "while travelling" or "on vacation." 18 % of the patients reported forgetting their GH injections "often" or "most of the times" when travelling or leaving home, with 12 % of the patients reporting to forget at least "occasionally."

Reasons for treatment refusal

Of the 70 respondents in our study 24 patients received no GHRT (34 %). Among six of these 24 patients, GHRT was stopped by their treating physicians. The reasons listed for stopping treatment were tumour recurrence/growth in 4 cases, hyperglycaemic dysregulation in one case and one patient stopped GHRT after suspected apoplexy. The other patients refused GHRT for various non-medical/personal reasons. The most common reason why these patients refused GHRT was fear of side effects (n = 9). It was also mentioned that the benefit of GHRT was considered insignificant (n = 6), and some patients did not feel well informed about GHD and its treatment (n = 5). Four of the five patients who reported feeling uninformed also indicated they were fearful of adverse effects. Two patients stated that the daily injections were too uncomfortable.

Perceived GH effects

A majority (76 %) of the patients receiving GHRT stated they didn't notice any differences during the day whether they had or had not injected GH on the evening before; 22 % stated feeling better. Although in the long term, 42 % noticed a significant difference, with only 9 % reporting they did not (49 % "did not know"). As expected, currently untreated patients differed significantly and negated a feeling of efficacy (p = 0.002). About half (52 %) of all participants estimated that GH therapy has a strong impact on their health and QoL, whereas only 8 % considered this as negligible or non-existent (40 % couldn't say). Again, patients receiving active treatment were more optimistic about the effects of therapy than untreated patients (strong impact 61 vs. 32 %; p = 0.012). Correspondingly, almost half (47 %) of the participants judged the effect of GH therapy on their body shape and appearance as positive, 11 % as negative, and 42 % did not perceive an effect.

Knowledge of GHD

34 participants (49 %) could not provide any correct symptom of GHD. Of the remaining patients (n = 36) a majority stated impairment of performance (n = 26). Additional mentioned symptom categories were abnormal body composition (n = 19), reduced QoL and other psychological disturbances (n = 11), altered lipid and glucose metabolism (n = 10), reduced bone mineral density (n = 10), increased cardiovascular risk (n = 3), and increased mortality (n = 1). The mean GHD knowledge score was 1.1 ± 1.4 (range: 0–4).

Attitudes towards LAGH therapy

When asked whether or not patients would want to start or switch to a LAGH that was administered once weekly 36 % of the patients responded affirmatively and 44 % considered the possibility to do so. 20 % indicated no interest. Of note, 12 of respondents had previously participated in a clinical trial with LAGH. When comparing answers, LAGH experienced patients significantly favoured switching to LAGH as compared to LAGH inexperienced patients (p = 0.048). Childhood-onset GHD (CoGHD) patients were more willing to make the switch than adult-onset (AoGHD) patients (57 % vs. 23 %; p = 0.031). Patients with and without GHRT were regarded separately. The willingness to switch or start such a treatment did not differ between patients receiving active daily GH therapy and untreated patients. Opinions about the risk of forgetting weekly administration were divided: 37 % considered the probability higher for weekly than for daily administration, 34 % considered it lower, and 28 % considered it equal. Patients without prior LAGH experience seemed to judge this risk higher than the study participants, although this failed to reach significance (p = 0.162). Similarly, treated patients seemed more wary than untreated patients

and estimated weekly injections to bear a higher risk of forgetting injections without reaching significance (p = 0.066). Of the LAGH study participants eight patients stated that weekly administration has had an advantage over daily administration, especially "less expenditure of time" and "fewer injections" were mostly named as beneficial effects. Two patients reported feeling better under LAGH therapy compared to conventional GHRT. Overall, 10 of the 12 LAGH patients preferred weekly injections, two preferred daily injections.

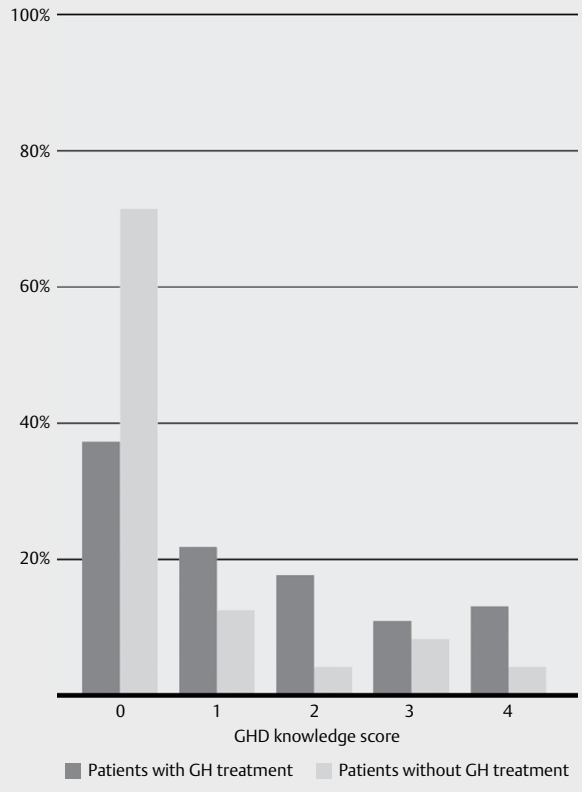
Parameters influencing adherence and treatment readiness

Adult- versus childhood-onset

There was no difference in treatment refusal or GHD knowledge score between AoGHD and CoGHD patients. Although treated CoGHD patients had worse non-adherence scores (mean 3.9 ± 3.3) than treated AoGHD patients (2.5 ± 2.2) the difference failed to meet the level of significance.

Level of education and knowledge of GHD

Patients receiving current GH treatment had significantly higher GHD knowledge scores as compared to untreated patients (1.4 ± 1.4 vs. 0.6 ± 1.2; p = 0.023), see ▶ **Fig. 1** for a histogram of the scores for both groups. Equally, the level of education (having obtained a level 3 degree according to the International Standard Classification of Education) was higher in treated patients (e. g., 29.5 % vs. 12.5 %; p = 0.017).



▶ **Fig. 1** Histogram depicting GHD knowledge scores of those patients with (dark grey) and those without (light grey) current growth hormone replacement therapy; higher scores indicate a better knowledge of the disease.

Discussion

In this study we surveyed growth hormone deficient patients regarding adherence, attitudes towards and beliefs about GHRT and knowledge of the disease. 76 % of our GHD patients currently under treatment were well adherent to it, with less than one missed injection per month. This result is well in agreement with the literature. Abdi et al. reported good adherence in 69 % (less than two missed injection per month) [21] , Rosenfeld and Bakker reported no missed injection during three months in 70 % of their patients [15].

However, 24 (34 %) of our survey participants were currently not receiving treatment or any GH substitution. Of those, 75 % had no clear medical reason for discontinuation of their treatment. Amongst the reasons mentioned were fear of side effects, low expectation of therapeutic benefits as well as lack of information about GHD and GHRT. A majority of patients refusing treatment did not believe GHRT influenced their health and/or QoL. Only two patients reported pain from the injections as a reason for discontinuation. Furthermore, we could show that knowledge of GHD is limited in these patients. Quintessentially, in most cases a lack of belief in treatment efficacy due to misinformation seems to precipitate unwillingness to pursue GHRT. This is in agreement with the results of Abdi et al., who described the perceived lack of therapeutic effect as the most common reason for discontinuation of GHRT [21]. It has previously been shown that generally adherence and patients' perception of disease severity strongly correlate [29]. As patients not receiving treatment had a lower level of education, it is to be suspected that in these patients the aptitude to comprehend their disease and the consequences of non-treatment is limited. To improve treatment of these patients, more focused educational and behavioural strategies may be needed [30–33].

We found no significant difference between patients with CoGHD as compared to AoGHD, even though the data indicates lower adherence in CoGHD patients. Adherence of GHRT has thoroughly been investigated in children, but only limited data are available in adult patients with CoGHD. In a recent study Auer et al. report higher adherence in AoGHD than CoGHD patients, but this finding was not independent of the age of the patient, indicating that younger patients independent of their age of onset are less adherent to therapy [23]. As our CoGHD cohort is older than in the study by Auer et al. this might explain the discrepancy of these results.

Willingness to initiate therapy with LAGH was lower than we predicted. Only 36 % of the respondents affirmed they would initiate treatment with a LAGH if it were available. This attitude towards LAGH did not differ between patients currently treated or not treated. That is possibly due to a sceptical or observing attitude regarding new pharmaceuticals and maybe more patients would opt for them when they have proven to be safe. Interestingly, CoGHD patients were more willing to make the switch than AoGHD patients. About a third each rated the probability of forgetting a weekly injection compared to a daily injection as higher, equal, or lower. This is particularly noteworthy because missing an injection of LAGH has a much bigger impact than missing an injection of daily GH. As a historic comparator one might think of bisphosphonates where switching from daily to weekly administration improved adherence [34, 35] and reduced the rate of discontinuation of therapy [35, 36].

12 patients were included in our survey who had previously gained first-hand experience with LAGH as participants of clinical trials. Over-

all, 10 of the 12 LAGH patients preferred weekly injections, two preferred daily injections. This might imply a selection bias of patients who are highly motivated to adopt novel therapies, but it might also indicate that the adoption of new therapeutic regimens necessitates its application. As this sample is small this can be only regarded as indicative data that need to be expanded on in larger studies.

Our data were collected using a self-reporting survey. That raises the problem of overestimating adherence, because patients might report better than actual adherence due to a feeling of guilt. Allowing them to fill and post the questionnaire completely anonymously was supposed to prevent that effect. This in turn disallowed us from comparing survey results with actual clinical data from the medical records so that we cannot.

A drawback of every retrospective survey is the risk of recall bias. An alternative and allegedly more objective method of assessing adherence is evaluating prescription data [37]. However, this method is prone to bias as well. E.g., it cannot be excluded that patients who indeed get their prescriptions regularly throw away leftover medication, do not correctly apply the medication or just don't have their prescriptions filled. It would have aided to identify false-positive reports of adherence in patients not receiving prescriptions, which we cannot exclude. Indeed, we emphasized opinions and beliefs about the benefits and discomforts of therapy which evaluation of prescription data cannot assess as is equally true for the assessment of adherence through measurement of metabolite levels. Moreover, IGF-I has been shown to be a poor marker for GHRT adherence because patients tend to inject GH more reliably prior to an appointment [23]. Hence, we determined a survey was the most eligible method of data collection for our approach.

A strength of our study is the high return rate and relatively large single center study population. It is also, to our knowledge, the first study to present data on attitudes towards LAGH. While in theory novel long-acting growth hormone formulations are expected to increase adherence [22] , patients seem to be wary to adopt it. and a small fraction seems to prefer staying on daily rhGH treatment. Long-term efficacy and safety of those new drugs, as well as their implication for costs and adherence, remain to be elucidated [38]. As Caicedo & Rosenfeld indicate, there are still some challenges in the delivery of growth hormone therapy to be overcome [39].

In conclusion, we could show that patients' educational level and beliefs regarding therapeutic effect is a strong driver of treatment adherence. Treating endocrinologists should identify patients refusing treatment and consider intensifying disease and treatment education. Furthermore, we demonstrated a reluctance of GHD patients to initiate treatment with LAGH. Patients with prior LAGH experience seem to be much in favour of these new drugs.

Conflict of Interest

FA and KS have nothing to disclose. JS has received lecture fees honoraria and grants from Novartis, Ipsen and Pfizer and grants from Chiasma and OPKO Health. He is also a consultant for Ipsen and Novartis. SS has received lecture fees honoraria and grants from Novartis, Ipsen and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Supplementary Material

▶ **Supplemental Table 1S** Questionnaire (translated from German).

Section A: Demographics
Sex: female / male
Age: ___ years
Highest level of education achieved: no school leaving certificate / "Hauptschulabschluss" (school leaving certificate after 9th or 10th grade) / "Mittlere Reife" (comparable to General Certificate of Secondary Education) / "Fachhochschulreife" (school leaving certificate permitting enrolment in university) / "Abitur" (matura, A-levels)
When were you diagnosed with growth hormone deficiency? as a child (<18 years old) / as an adult
Section B: Growth hormone therapy
Do you currently inject growth hormone? yes (continue with Question 1) / no (continue with next question)
Why don't you currently inject growth hormone? (multiple answers possible) I find the daily injection discomforting. / I deem the benefit of this therapy as not significant. / I feel not adequately informed in terms of disease and therapy. / I fear side effects. / Other reasons (free text); skip to Question 10
Question 1: How often do you forget your growth hormone injections? never / less than once per month / less than once per week / 2–3 times per week / more than 3 times per week
Question 2: How often do you forget your medication when traveling or spending the night elsewhere? never / seldomly / occasionally / often / mostly
Question 3: Have you injected growth hormone every single day in the past 7 days? yes / no
Question 4: At what time of day do you inject growth hormone? in the morning / at noon / in the evening
Question 5: Do you skip injections when feeling healthy and having the feeling that your symptoms are well controlled? never / seldomly / occasionally / often / mostly
Question 6: Do you sometimes skip injections when you're sick? never / seldomly / occasionally / often / mostly
Question 7: How do you feel the following day after injection? better than without injection / unchanged / worse than without injection
Question 8: Have you ever injected less than recommended or nothing at all because of feeling worse after injection? never / seldomly / occasionally / often / mostly
Question 9: Do you notice any differences when injecting or not injecting growth hormone in the long term? yes / no / I don't know
Question 10: Do you feel burdened by the growth hormone treatment? yes / no / occasionally
Question 11: In the foreseeable future, long-acting growth hormone preparations for weekly injection will be available. Would you then choose to switch your existing treatment / start a treatment with those new preparations? yes / no / maybe
Question 12: How do you estimate the risk of forgetting growth hormone injections when scheduled weekly compared to daily administration? higher / equal / lower
Question 13: How do you personally judge the influence growth hormone treatment has on your health, well-being and quality of life? little / I don't know / big
Question 14: How do you judge the effect of growth hormone treatment on your body shape and appearance? no influence / positive influence / negative influence
Question 15: Have you ever participated in a clinical trial with long-acting growth hormone? yes (continue with Question 16) / no (skip to section C)
Question 16: In your opinion, did the weekly application have an advantage over daily injections? yes, namely _____ (free-text) / no
Question 17: How did you feel during the weekly growth hormone treatment compared to your previous experience with daily injections? better than under the daily growth hormone regimen / unchanged / worse than under the daily growth hormone regimen
Question 18: If you could choose, which preparation would you prefer? A growth hormone preparation for daily injection / A growth hormone preparation for weekly injection
Section C: Knowledge of growth hormone
Growth hormone deficiency is a rare and not well-known disease. Please indicate any effect on health you may know of this disease: _____ (free-text)