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ORIGINAL ARTICLE

Is insulin-like growth factor-I a good marker for treatment adherence in growth hormone deficiency in adulthood?

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Summary

Objective There is a paucity of studies on adherence to growth hormone treatment in growth hormone deficient (GHD) adults. Therefore, this study reports on adherence to GH-replacement therapy in adults with GHD, with a special focus on the course and potential predictors of nonadherence.

Design Retrospective single-centre cohort study.

Patients From the local patient database, 179 suitable patients with GHD were identified.

Measurements The primary outcome was adherence assessed by calculating the percentage of available prescription data in comparison with recommended GH dosages over a mean follow-up period of 92·4 months. Patients were categorized into five adherence categories ranging from <20% to >80%.

Results Mean overall adherence was 74·0%, with 52·9% of patients falling into the adherence group of >80% and 8·8% of <20%. There was a significant drop in adherence (9·8%) between the first and second years of treatment ($P < 0{\cdot}001$). Patients with childhood-onset GHD were significantly less adherent to GH treatment than patients with adult-onset GHD (62·0% *vs* 77·0%, $P = 0{\cdot}012$); however, this finding was no longer significant after including age as a covariate. Frequency of IGF-1 levels lying outside the age- and sex-specific reference range was not a good indicator for adherence.

Conclusion Although overall adherence was relatively high in our study sample, there is a significant amount of patients who should be regarded as nonadherent. This applies in particular to younger patients. Treating physicians should be aware of the fact that IGF-1 levels do not seem to be a good indicator for adherence.

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Introduction

Compliance to medical treatment usually refers to the willingness and ability of patients to follow the advice of their physician, including the use of prescribed treatment regimens as recommended.[1] The term 'adherence' is preferable nowadays, as it emphasizes the capability of the patient to follow treatment advice on an informed consent basis, which also includes the understanding of potential implications of nonadherence.[1] While in controlled clinical trials, adherence, primarily estimated according to vial counting protocols, is reported to be about 80–95%;[1] in daily clinical practice, adherence is estimated to be as low as 50%, depending on the definition used.[2] Low adherence results, on the one hand, in low treatment efficacy and, on the other hand, in increased health costs.[2] Adherence is usually better in acute disease states than in chronic, and in 'silent' disorders such as arterial hypertension, diabetes or dyslipidaemia.[3,4] Although, in the long run, these diseases may be associated with severe health problems, nonadherence to medical treatment does not necessarily lead to any acute physical consequences for the patient such as pain or feelings of discomfort, particularly when the patient has been used to the condition for several years.

It is therefore apparent that adherence problems may also apply to patients with growth hormone deficiency (GHD). Although there are a number of studies which have addressed this problem in GH-treated children and adolescents,[5,6] there is a paucity of studies with a focus on adherence to GH substitution in adults outside the setting of a clinical trial.[7,8] This is especially true for studies assessing compliance not by self-report[9,10] but by objective measures. In other chronic conditions, there does not seem to be a major difference in adherence rates between children and adults, which is primarily explained by the fact that parents usually take care of their child's treatment.[11] However, a critical period is adolescence and puberty, where young individuals strive for independence and a focus on the members of the usually healthy peer group results in a significant decrease in adherence rates.[12,13] In children and adolescents, adherence is reported to lie in the range of 5–82%.[6] Comparison of studies is, however, hampered by the fact that adherence is hard to measure and each approach such as pill/vial counts, patient self-reporting or drug assays has its advantages and disadvantages, while some approaches are only practically

applicable in the context of a clinical trial.[1] Nonadherence is also not uniformly defined and may extend from occasionally missing a single dose to taking few or no doses.

Compounding this situation, physicians tend to overestimate the degree of adherence in their own patient population;[14] nonobjective techniques of adherence assessment, such as patient interviews, may especially be limited by concerns on both sides with regard to the patient–physician relationship. In addition, it has also been demonstrated that patients tend to overestimate their degree of adherence.[13]

While in children, the primary outcome for GH treatment is final height and chronic nonadherence can be detected by problems with height velocity,[15] this is more difficult to assess in adults where the effects are subtler. IGF-1 may serve as a biomarker; however, it is not sensitive for GH deficiency, and therefore, many patients with documented GH deficiency by dynamic testing present with normal IGF-1 values before the initiation of therapy, albeit usually at the lower end of the normal range.[16] In addition, short-term GH injections several days before appointments may be enough to establish IGF-1 levels within the normal range.[17] Aside from missing treatment efficacy, if nonadherence is not suspected or is denied, this will result in both increases in recommended doses, potentially resulting in side effects if adherence behaviour suddenly changes, as well as increases in treatment costs.[2] Most studies outside the setting of a clinical trial do not systematically evaluate adherence.[18,19] Although the results of these studies may reflect clinical practice, this may affect the results and transferability of the conclusions drawn from that data.

The current study was conducted, firstly, to assess long-term adherence in adult patients with GHD according to objective measures by prescription data and, secondly, to identify potential markers of long-term adherence.

Subjects and methods

We identified all patients from our local database who had been treated in the endocrine outpatient clinic of the Max Planck Institute of Psychiatry in Munich, Germany, between 2000 and 2014, who suffered from GHD due to any cause of adult-onset growth hormone deficiency (AoGHD where GHD was diagnosed after the age of 18 years) as well as childhood-onset growth hormone deficiency (CoGHD where GHD was diagnosed during childhood or adolescence). We used the insulin tolerance test (ITT) with a GH cut-off level of <3 μg/l for adults, a <5 μg/l cut-off level in the transition period and the GHRH-arginine test with an initial cut-off level of <9·1 μg/l until 2002, which was later adapted to BMI-dependent cut-off values of 11·5 μg/l for those with a BMI <25 kg/m^2, 8·0 μg/l for a BMI of 25–30 kg/m^2 and 4·2 μg/l for those with a BMI >30 kg/m^2.

Patients were included if they had been prescribed GH-replacement therapy at least once, according to the corresponding file reports and database entries (N = 296). Data on prescriptions (amount, manufacturer, dosage in mg) were extracted from the local patient management software (Informed, Efringen-Kirchen, Germany), in which every prescription is automatically documented.

Reasons for exclusion from the analysis were as follows:

- Patients with AoGHD who had already been pretreated with GH before their first visit to our department (N = 82);
- No documented dynamic testing results either by GHRH/arginine or insulin hypoglycaemia testing (IHT) (N = 12); and
- Participation in a 12-month adherence improvement programme during the observation period (2012–2013) (N = 23).

This resulted in a final study population of N = 179 patients. Most patients were aged between 35 and 64 years (N = 101); a small group of patients were over 65 years old (N = 24) and 54 patients were aged between 18 and 34 years (Table 1).

Table 1. General characteristics of the study sample

	N	%
Total	179	100
Sex		
Men	89	49·7
Women	90	50·3
Onset		
Childhood	38	21·2
Adult	141	78·8
Mean age of first GH prescription	44·0 (18–82; SD 17·2)	
Age groups in years		
18–34	54	30·2
35–64	101	56·4
≥65	24	13·4
Mean follow-up in months (range with SD)	92·6 (4–168; SD 53·9)	
Type of device used		
Multi-use device only	127	70·9
Single-use device only	2	1·1
Both	44	24·6
Data not available	6	3·4
Diagnosis		
Nonfunctioning adenoma	71	39·7
Craniopharyngioma	20	11·2
Prolactinoma	10	5·6
Cushing's disease	12	6·7
Other pituitary lesions	32	17·9
Idiopathic	11	6·1
Congenital	11	6·1
Other	12	6·7
Number of hormonal deficiencies		
1	17	9·5
2	37	20·7
3	34	19·0
4	91	50·8
Hormonal deficiencies		
Somatotroph	179	100
Gonadotroph	150	83·8
Thyrotroph	124	69·3
Corticotroph	102	57·0
Antidiuretic hormone	51	28·5
IGF-1 at baseline		
Below reference range	77	43·0
Within reference range	96	53·6
Not available	6	3·4

This study was approved by the ethics committee of the Ludwig-Maximilian University, Munich, and was prepared in accordance with the ethical standards of the Declaration of Helsinki.

Outcome evaluation

Adherence per year during the first 3 years of the observation period as well as overall adherence was calculated as a percentage of prescribed GH dosage in relation to the recommended doses for the corresponding timeframe. The GH dosage was calculated by the GH prescriptions filled by individual patients during the observational period, whereas the recommended GH dose was calculated retrospectively according to the patient files.

A patient was regarded as lost to follow-up if:

- He or she had not renewed prescriptions within the first 12 months after having received the first prescription, and the cessation of therapy was not officially documented in the corresponding patient file. In this case, we did not calculate any adherence rates and we have only reported on the number of patients lost during the first 12-month follow-up period.
- There was a gap >401 days (365 + 10%) between two visits or documented prescriptions after the first 12 months of follow-up, and the cessation of therapy was not officially documented in the corresponding patient file. This approach was chosen to minimize the possibility that patients had seen another endocrinologist in the meantime, who provided them with GH prescriptions instead, leading to falsely low adherence rates. In this case, we only reported on overall adherence until dropout.

As not every patient in the clinical setting is seen in exact yearly intervals, but to still allow for separate analyses of the first 3 years of treatment, data on adherence rates per year were normalized to 365 days. To minimize the systematic error resulting from this approach, only prescription dates within a ±10% window were used (329–401 days) for adherence stratified by year. Otherwise we only reported on overall adherence during the follow-up period.

Adherence was stratified into five groups: ranging from very good adherence (81-100%), good adherence (61–80%), poor adherence (41–60%) to very poor adherence (21–40%) and nonadherence (<20%). Rates that were higher than 100% according to our calculation were truncated to 100% ($N = 21$), as overadherence is hard to interpret because it is not possible to distinguish between overuse or early refills, an approach that is acceptable according to other studies using similar techniques for estimation of adherence.[20]

We also documented how many IGF-1 values lay outside the age- and gender-specific reference range provided by the manufacturer in relation to the total number of IGF-1 measurements during the observation period. IGF-1 was measured by chemiluminescence with the Nichols Advantage System (Nichols Institute Diagnostics, San Clemente, CA, USA) until September 2006 and, currently, the Immulite 2500 (DPC Siemens, Eschborn, Germany).

Statistics

Statistical analysis was performed using PASW Statistics (formerly SPSS, IBM Corporation, NY, United States) version 21·0 for Windows. Results are reported as means with standard deviation. Normally distributed metric nominal variables were compared by independent samples *t*-tests in cases of two-group comparisons and by analysis of variance (ANOVA) for more than two groups. In the case of group differences, we used the Bonferroni–Holm procedure for correcting for multiple comparisons. Comparison of categorical variables was performed by χ^2 tests. Pearson's and Spearman's correlation analyses were performed to investigate relationships of potential influential variables with overall compliance, and multiple linear regression was carried using the entry method to investigate the relative contributions of selected variables identified in univariate analysis. A *P*-value of <0·05 was considered statistically significant.

Results

General characteristics

The sex ratio was almost equally balanced with 49·7% men and 50·3% women. Of the patients, 38 had CoGHD (21·2%) and 141 patients had AoGHD (78·8%). Mean age at first prescription was 44·0 years (18–82, SD 17·2) for all patients (CoGHD: 22·7 *vs* AoGHD: 49·8 years; $P < 0·001$). Most patients (70·9%) used multi-use injectable pens for GH administration while 24·6% had also been temporarily and additionally prescribed single-use devices. Two patients (1·1%) were only using such devices. The mean follow-up period was 92·6 months (SD 53·9). At baseline, in 43·1% of patients, IGF-1 levels without treatment were below the age- and gender- specific reference range, while in 53·8%, they lay within the reference range despite documented GH deficiency by dynamic testing procedures. In six patients (3·4%), baseline IGF-1 levels were not available. The aetiology of GHD and information on pituitary insufficiencies is presented in Table 1.

Adherence

Mean overall adherence was 74·0% (SD 28·2) for the complete observation period. Of the patients observed, 53·0% fell into the group of very good adherence (81–100%), followed by 17·9% in the good adherence group (61–80%). A further 13·2% of patients had compliance of 41–60%, whereas 9·3% and 6·6%, respectively, of patients were categorized as being very poorly (40–21%) or nonadherent (<20%). Of the patients observed, 23 patients (12·8%) were lost during the first 12 months of follow-up, 31 (17·3%) during the second year and 16 (8·9%) during the third year (Table 2). We further calculated the change in mean adherence rates during the first 3 years of treatment. The mean adherence rate during the first year of treatment was relatively high at 84·7%. There was a significant drop in adherence between the first and second years (drop of 9·8–74·9%, $P < 0·001$) but no significant further decrease between the second and third years (drop of 1·2–73·7%, n.s.). If we had

calculated compliance including all patients who had been lost to follow-up during the observation period according to our definition and regarded them as being nonadherent, adherence would have been reduced to 68·1% (first year), 54·9% (second year) and 60·8% (third year).

Cessation of therapy

Of all patients, 91 had officially stopped therapy during follow-up (58·3%) according to the patient files, primarily for re-evaluation purposes (54·9%). The mean time to cessation was 4·8 years (SD 3·6). Of these patients, 62·6% continued GH therapy after a temporary treatment pause while 31·9% remained untreated due to various reasons. Five patients (5·5%) were lost to further follow-up after treatment cessation (Table 3). Overall adherence or adherence during the first 3 years of treatment was not associated with the cessation of therapy or the re-uptake of therapy after a treatment pause (data not shown).

Adherence according to groups

Although adherence did not differ between sexes, more men were lost to follow-up during the first 12 months of treatment than women ($P = 0·003$). Those with CoGHD were less treatment adherent than patients with AoGHD (62·0% *vs* 77·0%; $P = 0·012$). In particular, more CoGHD patients were in the 21–40% adherence group and fewer were in the 81–100% group ($P = 0·029$) (Table 4). In univariate analysis, only age ($r = 0·239$, $P = 0·039$) and age of onset ($r = 0·248$; $P = 0·032$) were significantly correlated with overall adherence but not type of injection device, percentage of IGF-1 levels outside the reference range, ΔIGF-1 between baseline and first evaluation during follow-up, maximum GH-response during IIT or GHRH-arginine test at baseline, cause of GHD or number of pituitary insufficiencies (Table 5). In multiple regression analysis, the age of onset was no longer associated with overall adherence, if age was included as a covariate (Table 6). In line with this, although CoGHD patients were not more likely to be lost during follow-up, adherence in younger patients (<35 years) during the first 12 months of treatment at our department was lower than in the older patients (75·8% *vs* 88·6%; $P = 0·02$).

Table 2. Adherence measures

	%	SD
Mean overall adherence	74·0	28·2
Adherence per year		
Mean adherence 1st year	84·7	21·9
Mean adherence 2nd year	74·9	31·5
Mean adherence 3rd year	73·7	31·7
	N	%
Adherence in groups		
0–20%	10	6·6
21–40%	14	9·3
41–60%	20	13·2
61–80%	27	17·9
81–100%	80	53·0
Lost to follow-up		
First year	23	12·8
Second year	31	17·3
Third year	16	8·9

Table 3. Documented cessation of therapy during the follow-up period

	N	%
Documented cessation of therapy during follow-up	91	58·3
Mean time to cessation in months (range with SD)	57·7 (4·9–184·3, SD 43·6)	
Reason according to patient file		
Re-evaluation	50	54·9
Side effects	7	7·7
Low adherence	4	4·4
Other	5	5·5
Not documented	25	27·5
Re-uptake after cessation		
Yes	57	62·6
No	29	31·9
Unknown (lost to follow-up)	5	5·5

Discussion

In our patient cohort, about 50% of patients had adherence rates above 80%, while in approximately 30%, there was a discrepancy of more than 40% between the cumulative prescribed and recommended GH dosage. To date, there is a paucity of studies investigating compliance in the adult population. Rosenfeld and Bakker,[10] using a question-based self-report approach, reported that 34% of patients fell into the highly compliant category and 35% into the noncompliant segment according to their missing doses definition. The adherence rates found in our study were also in accordance with the literature for chronic diseases.[21] Reported adherence rates for the same disease may, however, vary substantially in the literature as they depend on the technique of adherence assessment.[1] The prescription-based approach in our study was chosen as it offers, in our eyes, the most objective way to assess treatment adherence and is applicable in the current setting as, in Germany, GH is not prescribed by general practitioners (GPs) or other specialists as it is a very costly treatment and physicians have to pay a fee if they exceed their allocated quarterly drug budget. Such a discrete and objective measure of adherence may help to preselect patients with poor adherence and open the discussion for causes of nonadherence, which include forgetfulness, side effects or missing treatment benefit.[1] A general problem is that nonadherence is generally imprecisely defined, as some authors regard patients with an adherence rate of less than 80% as being nonadherent[1] while others use a more treatment goal-oriented definition defined by the fact that 'the failure to comply is sufficient to interfere appreciably with achieving the therapeutic goal'.[22] It is hard to say what rate of adherence in GH treatment in adults is necessary to achieve a certain treatment goal as, in contrast to CoGHD, the goal itself is not universally defined. To date,

Table 4. Difference in adherence according to groups

	Sex					Age							Diagnosis				
	Female	SD	Male	SD	*P*	18–34	SD	35–64	SD	≥65	SD	*P*	CoGHD	SD	AoGHD	SD	*P*
Mean overall adherence (%)	77·1	24·9	71·1	30·8	0·2	66·3	30·2	76·7	27·2	82·1	21·3	0·1	62·0	29·0	77·0	27·0	**0·012**
Adherence 1st year	85·6	20·4	85·3	21·0	0·9	75·8	25·9	88·6	18·5	86·3	16·0	**0·02***	75·7	22·4	86·7	20·2	0·070
Adherence 2nd year	76·2	29·6	73·6	34·1	0·7	65·4	32·7	78·3	31·3	74·4	31·1	0·3	60·2	31·5	76·7	31·4	0·140
Adherence 3rd year	75·9	28·6	71·5	35·3	0·6	60·1	37·5	77·7	29·9	80·2	25·0	0·1	57·7	37·8	75·7	30·9	0·132

	N	%	*N*	%	*P*	*N*	%	*N*	%	*N*	%	*P*	*N*	%	*N*	%	*P*
Categories																	
0–20%	6	8·8	3	3·8	0·2	4	9·5	5	5·7	0	0·0	0·406	2	7·7	7	5·8	**0·029**
21–40%	9	13·2	5	6·3		7	16·7	6	6·8	1	5·9		6	23·1	8	6·6	
41–60%	10	14·7	10	12·7		5	11·9	13	14·8	2	11·8		3	11·5	17	14·0	
61–80%	7	10·3	19	24·1		9	21·4	15	17·0	2	11·8		7	26·9	19	15·7	
81–100%	36	52·9	42	53·2		17	40·5	49	55·7	12	70·6		8	30·8	70	57·9	
Lost to follow-up																	
During 1st year	5		18		**0·003**	8		9		5		0·194	8		15		0·089
During 2nd year	14		17		0·494	8		18		5		0·778	4		27		0·494
During 3rd year	8		8		0·922	3		11		2		0·871	2		14		0·845

*Adherence in the 18- to 34-year group *vs* the 35- to 64-year group. *P*-values < 0.05 are highlighted in bold letters.

Table 5. Univariate Pearson's and Spearman's correlation coefficients between overall compliance and potential influential factors

		Age	Sex	Age of onset	Number of pituitary insufficiencies	Diagnosis	IGF-1 below reference range at baseline	GH response*	IGF-1 at baseline	ΔIGF-1†	IGF-1 below reference range during follow-up (%)‡	Device
Correlation coefficient	Overall compliance	0·239	0·041	0·248	0·051	0·05	−0·019	−0·003	−0·021	0·197	0·016	0·065
P-value		**0·039**	0·73	**0·032**	0·662	0·67	0·869	0·977	0·881	0·289	0·892	0·437

*Maximum growth hormone response during insulin tolerance test (ITT) or GHRH/arginine-stimulation. Separate analysis of the two tests yielded comparable results.
†Difference between baseline IGF-1 and IGF-1 at first re-evaluation visit within the first 12 months of treatment.
‡Percentage of IGF-1 values lying below the reference range during follow-up in those with subnormal IGF-1 levels at baseline.

there is no reliable and widely accepted marker available that facilitates evaluation and adjustment of GH dosages in AoGHD, although a score has been proposed to assess treatment response.[23] In our clinic, we usually aim to achieve IGF-1 levels within the age- and gender-specific reference range but always in the context of preventing any side effects and taking into account the subjective benefits for the patient. Despite this approach, IGF-1 levels and the frequency of IGF-1 levels below the age- and gender-specific reference range did not seem to be good markers for assessing adherence.

In our sample, 53·6% of all patients had IGF-1 levels within the normal 2-SDS range, despite confirmation of GHD by dynamic testing. Even after excluding those with IGF-1 levels in the normal range before initiation of treatment, suboptimal IGF-1 levels were not a good measure to detect nonadherence. This may be explained by the well recognized fact that many patients improve their medication-taking behaviour several days before the appointment with their physician – also known as white-collar adherence[13,16] – which, in the case of GH substitution, may be sufficient to significantly raise IGF-1 levels.[16,24] In particular, male response in IGF-1 levels to GH administration occurs quickly[17] and nonadherence may therefore be masked by adequate administration for only a few days before the next appointment. Keeping this phenomenon in mind, individual changes in IGF-1 levels from baseline (delta IGF-1) also seem to be rather unreliable markers of adherence. Assessing treatment adherence by IGF-1 in the elderly population may be even more difficult, as there is a significant overlap between GH deficiency and age- and gender-matched controls, and only 21% will present with IGF-1 levels below the reference range.[25] In these patients, a target

Table 6. Results of the models obtained by multivariate linear regression analysis

Model	β	SE	*P*-value	Confidence interval (CI) (95·0%)	
				Lowest	Highest
Model 1					
Sex	6·288	4·556	0·17	−2·718	15·293
Age of Onset	13·639	5·854	**0·021**	2·068	25·209
Model 2					
Sex	8·44	4·759	0·078	−0·969	17·848
Age of onset	7·057	7·305	0·336	−7·385	21·498
Age of first GH prescription	0·263	0·176	0·137	−0·085	0·611

IGF-1 value for treatment evaluation is even less helpful than in those with low IGF-1 levels. This is aggravated by the fact that although daily IGF-1 variation is expected to be relatively low, it can be affected by variability in the time interval between administration and measurement[26] and individual response is highly variable.[27] In children, for example, a 15-fold variation in the GH doses required to maintain IGF-I levels within the reference range has been reported,[28] underlining the fact that discrimination between low IGF-1 levels due to nonadherence or other influential factors such as age, height, oral oestrogen intake or BMI is difficult.[29] The fact that IGF-1 levels may be measured less frequently in clinical practice than in clinical studies may leave a significant gap of unsupervised time.

We demonstrated that patients with CoGHD were significantly less compliant than those with AoGHD. However, 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. It has been reported before that, in the adolescent period, adherence is significantly worse than in children.[10] To our knowledge, there is no other study that has separately investigated adherence beyond the age of 18 years in adults with CoGHD or in a group of young adults. Rosenfeld and Bakker reported in their survey that teenagers are the least compliant age group.[10] According to this study, the rate of those patients falling into the lowest two adherence quartiles was 77% for teens and 65% for adults. However, our results are not directly comparable and, in particular, there was no explicit reporting on subgroups with CoGHD *vs* AoGHD. We have shown before that up to 50% of adolescents are lost during transition from the paediatric to the adult endocrinologist.[30] The investigated cohort is therefore already preselected with regard to acceptance of continuation of GH treatment. CoGHD patients, as demanded by national healthcare providers, usually undergo treatment pause and repeat dynamic testing at their first visit to our department. We cannot exclude the possibility that their former uses and experiences with GH treatment affected our results.

There was no significant difference in overall compliance between sexes and the percentage of men and women with compliance >80% was equally high. For other chronic conditions, sex has also not been associated with levels of adherence.[20,31] However, significantly more men were lost during the first 12 months of follow-up.

Regarding adherence over time, there was a significant drop by an average of 10% in overall adherence between the first and second years of GH treatment, not accounting for those who were excluded from further analysis either because they were lost during follow-up within the first 3 years or they did not receive any follow-up prescriptions. After the second year, overall adherence remained relatively stable and did not significantly differ from overall adherence during the mean follow-up period of 8 years. In keeping with this, according to unpublished data from the National Cooperative Growth Study, there seemed to be a significant drop in prescription refill during the first 11 months of treatment.[32]

One strength of our study is that we investigated long-term adherence assessed by objective measures in a large, single-centre, clinically well-defined patient cohort. This is also, to our knowledge, the first published study proving a separate analysis of CoGHD and AoGHD with regard to adherence and it is also unique in its detailed approach for investigating the dynamics of adherence to GH treatment in adults over time. A limitation is the rather indirect approach calculating adherence retrospectively from prescription data. Although analysis of prescription data has shown good concordance with other adherence measures,[33] it does not determine delay or failure in dose administration and it is also not possible to detect failure to encash prescriptions. We also do not know whether patients who had been lost to follow-up had continued their treatment at another endocrine practice or stopped treatment completely. Lastly, we cannot guarantee the generalizability of our results as individual factors such as the physician–patient relationship and the quality of patient education is known to have a huge impact on adherence, and these factors may differ between different centres in different countries.

In conclusion, we have demonstrated that IGF-1 levels are not a good predictor of adherence to GH treatment in adult patients with GH deficiency. While there was a significant drop in adherence between the first and second years of treatment, adherence seemed to remain stable thereafter. Younger adults seem to need particular attention with regard to treatment adherence. Physicians might need to consider combining different approaches for evaluating adherence in their patients, using self-report and medication count rather than biochemical assessment alone.

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