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Adherence to growth hormone therapy in children and its potential barriers

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Abstract

**Background:** One of the main concerns in chronic diseases such as growth hormone (GH) deficiency is adherence to the treatment, which significantly affects treatment outcomes.

**Methods:** This cross-sectional study was conducted among 169 GH recipient children (2–12 years) and teens (13–19 years) referred to a GH distributing teaching pharmacy. The eight-item Morisky Medication Adherence Scale (MMAS) and auto-compliance method were used for the assessment of patients’ adherence to GH. The potential barriers to GH therapy adherence and medication persistence were also explored.

**Results:** Based on the MMAS method, 56.7% of the children and 57.9% of the adolescent groups were adherent to GH therapy. Conversely, according to the auto-compliance method almost all the patients were adherent in the children (95.2%) and adolescent (95.5%) groups. Forgetting to take the injection or refill the prescription, being away from home, exhaustion from long-term injection, drug shortage and inaccessibility to the pharmacy were barriers found to be significantly associated with a low adherence in the children group. While in the adolescent group, forgetting to take the injection, painful injection, concern about long-term complications and exhaustion from long-term injection revealed a significant association with low adherence. Persistence with GH therapy was reported in 75.3% and 67% of children and adolescent patients, respectively.

**Conclusions:** The current study revealed that overall adherence of the study population is low. Considering the barriers with significant association with adherence, different strategies can be incorporated to enhance adherence to GH therapy, i.e. providing early patient and parent education and support, medication reminder systems and longer duration of GH prescriptions.

**Keywords:** adherence; children; growth hormone.

Introduction

Exogenous growth hormone (GH) replacement therapy has been prescribed for many year the treatment of idiopathic short stature, in short children born small-for-gestational age (SGA) and for short stature state related to Turner’s syndrome and for many GH deficiency disorders in children and adults [1, 2]. The nature of these conditions is such that patients require long-term drug therapy. Hence, the patient’s medication adherence has a crucial role in the treatment’s success rate. Furthermore, available evidence indicates that a patient’s persistence in chronic conditions considerably reduces after 6 months of treatment [3, 4]. Based on previous studies, adherence to GH therapy ranges from 5% to 82% [5]. Non-adherence to therapy may vary from omitting a dose intermittently, to taking a small number or even no dose of medication at all [6].

It has been shown that growth velocity is significantly lower in children with poor adherence to GH therapy compared to those with higher adherence [7, 8].

In order to reduce injection barriers, GH injection devices have evolved over the years from traditional syringe and needle systems to advanced pen injection systems which are associated with improved adherence [9, 10]. Injection pens are easier to use, more accurate and accepted by the patients than conventional syringes [11, 12]. It has been shown that adherence would be improved in children who were trained by clinical staff and have chosen the type of injection devices themselves [13].

Despite the availability of these technologically advanced devices, further measures should be taken to improve patients’ adherence. From a financial point of view, GH remains a costly treatment, which is an additional dilemma [14].
Several studies have reported some factors related to patients’ adherence, including initial inadequate understanding of the treatment goals [15], frequent subcutaneous injections [10], long-term treatment [9], dissatisfaction with treatment results [16] and socio-economic status [17]. Moreover, a number of studies have suggested that patients’ adherence to treatment could be a multi-factorial phenomenon.

In addition, poor adherence to drug therapy has resulted in both reduced clinical outcome and increased cost of care [18].

Nevertheless, there is limited information about the rate of poor adherence to GH therapy and the potential barriers to GH injection in developing countries. Therefore, the current work was designed to assess children’s adherence to GH therapy. Moreover, the underlying factors that may predispose the patients to low adherence were investigated to guide health care providers to design proper strategies to promote patients’ adherence and improve clinical outcomes.

Materials and methods

This cross-sectional study was conducted among 169 children on GH therapy (aged 2–19 years) referred to a GH distributing pharmacy, affiliated to the Tehran University of Medical Sciences (TUMS). The participants were interviewed by the means of telephone calls. The qualitative content validity of the questionnaire was assessed prior to the study implementation by asking eight endocrinologists to determine the relevancy, simplicity and clarity of the questionnaire items. The reliability of the questionnaire was confirmed by a test-retest study which was done on 20 participants. The patients were asked to complete the questionnaire twice at 2-week intervals. Then the Cronbach’s α was calculated as 0.697, which confirmed the reliability of the questionnaire.

The Ethical Committee of TUMS approved the study protocol and verbal informed consent was obtained from the participants (patients and/or parents) prior to the interview.

Following the registration of demographic characteristics, the eight-item Morisky Medication Adherence Scale (MMAS) was used for the assessment of patients’ adherence to the GH therapy [19]. The questionnaire items were scored as 0 (Yes) or 1 (No), except for items five (No scored as 0 and Yes scored as 1) and eight (never/rarely scored as 1 and once in a while/sometimes/usually/all the times scored as 0). According to MMAS, a patient was considered highly adherent if he/she received a score of 8, while scores 6.0–7.9 and <6 were categorized as medium and low adherence, respectively [20].

Moreover, adherence to GH therapy was also measured by the auto-compliance method. This method estimates the number of missed GH injections during the previous month, following the methodology designed by Haynes et al. [21].

In the auto-compliance method, adherence was measured by dividing the total number of GH injections by the total number of prescribed GH injections during the last month and was reported as a percentage. Patients who declared taking more than 80% of the total number of the prescribed GH injections were considered as adherent to GH therapy [22].

The probable barriers to GH therapy adherence were assessed by a questionnaire, which was designed based on the reported results of the Rosenfeld et al. study [23].

Sixteen questions were applied to assess the possible barriers which may result in missed doses. The following scale was used for patients’ responses: 1 = always, 2 = sometimes, 3 = seldom, 4 = never. Finally, we measured the total score of barriers and compared the correlation between the barrier score and adherence levels.

At the end of the questionnaire the patients’ persistence with the GH therapy were reviewed. Non-persistence was considered as discontinuation of GH injections for at least 1 month during the treatment period.

Statistical analysis

Data was analyzed using SPSS 16 software (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequency (percentage). The χ²-test was used to analyze categorical data. The association between the level of adherence and continuous variables was assessed by an independent sample t-test for parametric variables and the Mann-Whitney U-test for non-parametric variables. A p-value <0.05 was considered as statistically significant.

Results

The participants consisted of 81 (47.9%) children (2–12 years) and 88 (52.1%) teens aged 13–19 years. The demographic variables of the patients are shown in Table 1.

Adherence

Using MMAS, 16.6% of patients had high adherence, while 40.8% and 42.6% of them had intermediate and low adherence, respectively. In children 14.8% of the patients had high adherence to GH, whereas 42% and 43.2% had intermediate and low adherence, respectively. Among the adolescents, 18.2% were highly adherent to GH therapy while 39.8% and 42% had intermediate and low adherence to GH therapy. The frequency of answers to each MMAS question is presented in Table 2.

There were no significant differences in each level of adherence between the two age groups (p-value = 0.49). Considering high and intermediate adherence levels as acceptable adherence, 56.7% and 57.9% of the children and adolescents were adherent, respectively, in the current study.
Based on the self-reporting method, 95.3% of the patients declared to have an acceptable adherence to GH therapy.

There was no significant relationship between parents’ level of education and adherence in patients for whom their parents injected the medication.

GH injection by parents was more common in children than in adolescent patients (p < 0.001). There was no significant difference in barriers among the study groups except due to financial problems, which was reported more frequently by parents in the children group than in the adolescent group (p = 0.04).

The association between patients’ adherence to GH therapy and possible factors and barriers

The potential barriers affecting patients’ adherence to GH therapy are listed in Table 3.

Forgetting to take the injection or refill the prescription, being away from home, exhaustion from long-time injection, drug shortage and inaccessibility to the GH distributing pharmacy were barriers with significant association with low adherence in the children group.

While in the adolescent group forgetting to take the injection, painful injection, concern about long-term
complications and exhaustion from long-time injection showed a significant association with low adherence.

The relationship between probable barriers and GH adherence in the study groups are shown in Tables 4 and 5.

Based on the Mann-Whitney U-test, no significant association was detected between the duration of GH injection and adherence in the children (p = 0.78) and adolescent (p = 0.67) groups.

The total barrier score had a significant relationship with adherence in the studied population (53.55 ± 5.6 and 50.45 ± 5.1 in the acceptable and poor adherence groups, respectively [p < 0.001]).

Persistence to GH therapy was reported in 75.3% and 67% of the children and adolescent patients, respectively.

**Discussion**

One of the main concerns in chronic diseases such as GH deficiency is adherence to the treatment, which significantly affects treatment outcomes.

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**Table 3**: Probable barriers to GH therapy adherence in the studied groups.

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Total (n=169)</th>
<th>2–12 years (n=81)</th>
<th>13–19 years (n=88)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgot to take the drug</td>
<td>16 (9.5%)</td>
<td>9 (11.1%)</td>
<td>7 (8%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Forgot to refill</td>
<td>7 (4.1%)</td>
<td>5 (6.2%)</td>
<td>2 (2.3%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Physician inaccessibility</td>
<td>3 (1.8%)</td>
<td>2 (2.5%)</td>
<td>1 (1.1%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Experienced adverse effects</td>
<td>9 (5.4%)</td>
<td>5 (6.2%)</td>
<td>4 (4.6%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Cost</td>
<td>86 (51.8%)</td>
<td>47 (58%)</td>
<td>39 (44.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Being away from home</td>
<td>29 (17.2%)</td>
<td>15 (18.5%)</td>
<td>14 (15.9%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>17 (10.1%)</td>
<td>8 (9.9%)</td>
<td>9 (10.2%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Dissatisfaction with treatment results</td>
<td>46 (27.7%)</td>
<td>23 (28.4%)</td>
<td>23 (27.1%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Negative attitude of friends or family</td>
<td>1 (0.6%)</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Painful injection</td>
<td>28 (17.2%)</td>
<td>15 (19.2%)</td>
<td>13 (15.3%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Unable to inject (patient and caregiver)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>3 (3.4%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Concern about long-term complications</td>
<td>70 (41.1%)</td>
<td>36 (44.4%)</td>
<td>34 (38.6%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Exhausted from long-term injections</td>
<td>60 (35.5%)</td>
<td>32 (39.5%)</td>
<td>28 (31.8%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>25 (14.8%)</td>
<td>10 (12.3%)</td>
<td>15 (17%)</td>
<td>0.26</td>
</tr>
<tr>
<td>GH shortage</td>
<td>80 (48.5%)</td>
<td>39 (48.1%)</td>
<td>41 (48.2%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Inaccessibility to GH distributing pharmacy</td>
<td>82 (49.2%)</td>
<td>42 (52.5%)</td>
<td>40 (47.1%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data are expressed as number (%). p-Value <0.05 was considered significant.

**Table 4**: The relationship of probable barriers and GH adherence in children (2–12 years).

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Low adherence (n=35)</th>
<th>Intermediate/high adherence (n=46)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgot to take the drug</td>
<td>8 (22.9%)</td>
<td>1 (2.2%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Forgot to refill</td>
<td>5 (14.3%)</td>
<td>0 (0%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Physician inaccessibility</td>
<td>1 (2.9%)</td>
<td>1 (2.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Experienced adverse effects</td>
<td>2 (5.9%)</td>
<td>3 (6.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Cost</td>
<td>23 (65.7%)</td>
<td>24 (54.5%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Being away from home</td>
<td>12 (34.3%)</td>
<td>3 (6.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>2 (5.7%)</td>
<td>6 (13%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Dissatisfaction with treatment results</td>
<td>13 (37.1%)</td>
<td>10 (21.7%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Negative attitude of friends or family</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Painful injection</td>
<td>8 (24.2%)</td>
<td>7 (15.6%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Unable to inject (patient and caregiver)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Concern about long-term complications</td>
<td>19 (54.3%)</td>
<td>17 (37%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Exhausted from long-term injections</td>
<td>19 (54.3%)</td>
<td>13 (28.3%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>5 (14.3%)</td>
<td>5 (10.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>GH shortage</td>
<td>22 (64.7%)</td>
<td>17 (37%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are expressed as number (%). p-Value <0.05 was considered significant.
In the present study, intermediate to high adherence to GH therapy based on Morisky medication adherence in the children and adolescent groups were 56.7% and 57.9%, respectively.

Conversely, according to the auto-compliance method almost all the patients were adherent in the children (95.2%) and adult (95.5%) groups. The difference in the results of these two evaluation methods which were also reported in previous studies [24, 25] may be in part due to the fact that the self-reported methods are subject to patients recall bias, fear of disappointing health care providers, eluding confrontation or a combination of those [5]. Because the eight-item Morisky scale applies more indirect questions it might be less affected by the mentioned factors compared to the auto-compliance method.

In spite of the usefulness and non-expensive self-reporting methods in evaluating medication adherence, they have low sensitivity for the non-adherence group [5]. Consequently, we may have overestimated adherence. However, the eight-item Morisky scale with reported sensitivity of 93% and specificity of 53% is considered as a useful tool to assess the treatment adherence in a clinical setting [20].

Although there is no gold standard method to measure adherence, a review of prescription records might be the preferable method. However, we did not have such records for our population.

Rosenfeld et al. [23] assessed 882 patients receiving or previously treated with GH using a questionnaire completed by patients and/or their parents. Adherence assessment was based on the responses to nine potential reasons for missing GH doses. They reported that non-adherence to GH therapy varied from 64% in children (4–12 years), to 65% in adults (over 18 years) to 77% in teens (13–17 years). They found that displeasure with treatment outcome, unawareness of the importance of missed doses, painful injection and inadequate rapport with their health care provider may have considerable association with non-adherence.

Rees [16] conducted a study on 29 patients (7–20 years of age) with renal disease who were receiving GH therapy. A questionnaire was filled by the patients or their parents to assess patients’ adherence to GH therapy. The level of non-adherence was defined by number of missed injections. The results revealed that 38% of patients never missed an injection, whereas 55% missed one to five injections per week and 7% missed five to 10 injections per month.

The non-adherence rates of these two studies were higher than in our study, which may be due to variations in terms of methods, sample size and population.

In the present study, no relationship was found between the parents’ level of education and adherence in patients for whom their parents injected the GH. Farsaei et al. [24] reported similar results in patients with diabetes receiving insulin injections.

In contrast with our results, Gács and Hosszu’s study [17] showed that there is significant association between father’s educational level and adherence to GH therapy in idiopathic GH deficient children (p < 0.001). Interestingly,

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Low adherence (n = 37)</th>
<th>Intermediate/high adherence (n = 51)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgot to take the drug</td>
<td>7 (18.9%)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Forgot to refill</td>
<td>1 (2.7%)</td>
<td>1 (2%)</td>
<td>1</td>
</tr>
<tr>
<td>Physician inaccessibility</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1</td>
</tr>
<tr>
<td>Experienced adverse effects</td>
<td>3 (8.1%)</td>
<td>1 (2%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cost</td>
<td>20 (55.6%)</td>
<td>19 (37.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Being away from home</td>
<td>7 (18.9%)</td>
<td>7 (13.7%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>2 (5.6%)</td>
<td>7 (13.7%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dissatisfaction with treatment results</td>
<td>11 (32.4%)</td>
<td>12 (23.5%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Negative attitude of friends or family</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Painful injection</td>
<td>10 (28.6%)</td>
<td>3 (6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Unable to inject (patient and caregiver)</td>
<td>2 (5.4%)</td>
<td>1 (2%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Concern about long-term complications</td>
<td>19 (51.4%)</td>
<td>15 (29.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Exhausted from long-term injections</td>
<td>18 (48.6%)</td>
<td>10 (19.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>7 (18.9%)</td>
<td>8 (15.7%)</td>
<td>0.45</td>
</tr>
<tr>
<td>GH shortage</td>
<td>14 (38.9%)</td>
<td>27 (55.1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Inaccessibility to GH distributing pharmacy</td>
<td>14 (38.9%)</td>
<td>26 (53.1%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Data are expressed as number (%). p-Value <0.05 was considered significant.
Rosenfeld et al. [23] reported that parents of highly compliant children had a lower educational level.

In our study, there were no significant differences in each level of adherence between the two age groups. While, Rosenfeld et al. [23] found a lower adherence level in the teen group (23%) in comparison with the children (36%) and adult groups (34%).

In various studies, the association between several factors and poor adherence has been reported including: adolescent’s age group [23], use of conventional syringe instead of automatic pen devices [26], longer duration of GH therapy [7, 26], injection not given by the patients [26], lower socio-economic status [17] and dissatisfaction with treatment results [23]. In contrast, other studies showed no association between factors such as age [8, 26], socio-economic status [26], duration of treatment [27], injection giver [16], type of injection device [28] and medication adherence. These discordant results may be due to different methodology and study populations. We also did not find any association between adherence and factors such as age, gender, GH therapy duration and injection giver.

We found significant association between missing taking an injection or refilling the prescription and adherence; however, the sample sizes were low and can lead to the reduced precision of the analysis. Aydın et al. [29] reported that missing renewing the prescription and administering GH were the main causes of the injection omissions.

To overcome these barriers, patient medication reminder systems, longer duration of GH prescription refills, less frequent pharmacy visits and family support can be helpful.

Among the adolescent group in our study, one of the significant barriers to GH therapy was patients’ concerns about long-term therapy (p = 0.03), which may be due to insufficient patient counseling. Therefore health care professionals should discuss with patients and their families about the potential adverse effects and the overall safety of GH therapy.

Misconception about the consequences of injection omissions is one the potential reasons for non-adherence. Hence, early patient and parent education and training are essential. Effects of GH adherence on the mean final height and prevention of probable future complications such as cardiovascular complications are areas that need to be covered in counseling sessions [30, 31].

It has been shown that prefilled, disposable and easy to use pens make them more popular and putative by the patients [32, 33].

Several studies have indicated that pen injection devices are associated with improved treatment adherence compared to conventional vials and syringes [26, 34]. Likewise, giving patients a choice of injection device may improve adherence [35].

A majority of our patients (97%) used pens as their injection device, so the type of injection could not be considered as a possible barrier to GH therapy in the current study. However, there are limited types of pen devices available in our country (Iran) and patients do not have the opportunity to choose their injection device.

Although GH is a very expensive medication, we did not find a significant association between cost and adherence. This may be due to the fact that in almost all the studied patients (99.4%) GH was under coverage of insurance companies and the out of pocket expense was only 10% of the drug cost.

GH therapy requires regular daily subcutaneous injections which would alter the level of adherence. In recent years, safety and efficacy of several sustained-release GH formulations with once a week administration have been evaluated [36, 37]. Hence, preparation of long-acting GH formulations can offer a significant improvement in adherence [38].

In the current study, GH persistence was more common in adherent patients, especially in the children group, which may signify that barriers might be common to both practices.

Conclusions

Non-adherence can cause suboptimal response to GH therapy and mislead the clinical team regarding the efficacy of treatment [8]. Availability of adherence data to medical practitioners would be helpful to improve adherence. Early identification of barriers to the adherence and effective interventions are essential. Furthermore, multifaceted causes for poor adherence require a great variety of interventions.

The current study revealed that overall adherence of the patients is low. Considering the barriers with significant relationship with adherence, different strategies can be implemented to enhance adherence to GH therapy, i.e. providing early patient and/or parent education and support, medication reminder systems and longer duration of GH prescriptions.

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted
manuscript and approved submission. All authors contributed to developing the study protocol. In addition, Shahrazd Mohseni analyzed the data and drafted the initial manuscript. Zahra Heydari interviewed the study participants and collected the data. Mostafa Qorbani contributed to data analysis and interpretation of results. Mania Radfar supervised the whole project, contributed to interpretation of the results and revised the manuscript.

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**Employment or leadership:** None declared.

**Competing interests:** The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to Submit the report for publication.

**References**