Identifying Potentially Modifiable Factors Associated with Treatment Non-Adherence in Paediatric Growth Hormone Deficiency: A Systematic Review

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Keywords

Growth hormone deficiency · Recombinant human growth hormone treatment · Adherence · Systematic review

Abstract

Background: Despite the developments of recombinant growth hormone (rhGH) treatment and the benefits in long-term clinical health outcomes, evidence has shown that many children with growth hormone deficiency (GHD) still fail to achieve their target adult height. Suboptimal outcomes have been largely attributed to treatment non-adherence. **Methods:** A search of 11 electronic databases was undertaken to identify relevant articles, published in English, between 1985 and 2018. Additional search strategies included hand-searching topic review articles to identify eligible studies. Articles were screened against the inclusion eligibility criteria and data on sample characteristics, study design, outcomes, and key findings was extracted. The results were narratively synthesised and categorised using the COM-B theoretical framework. **Results:** Twenty-one full-text articles were assessed for eligibility, of which 6 articles met the inclusion criteria. The prevalence of non-adherence in the included studies varied from 7 to 71%. Potentially modifiable factors associated with rhGH non-adherence were categorised

within the COM-B framework; key factors included: a lack of knowledge and understanding of the condition and treatment, discomfort and pain associated with injections, and the quality of the healthcare professional-patient relationship. **Conclusion:** This review highlights the scope of the adherence problem evident amongst the paediatric GHD population and in addition presents the wide range of potentially modifiable factors that explain this health-related behaviour.

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Introduction

Background

Despite the developments of recombinant growth hormone (rhGH) treatment and the benefits in clinical health outcomes, several studies have shown that many children with growth hormone deficiency (GHD) still fail to achieve their target adult height [1–6]. Suboptimal outcomes have been largely attributed to the failure of patients/caregivers to maximally adhere to the prescribed treatment with respect to initiation, implementation (i.e., dosage, frequency), and duration [7–10]. Several studies have observed marked variations in reported levels of ad-

herence amongst children given rhGH treatment [4, 7, 11, 12]. For example, the systematic review conducted by Fisher and Acerini [4] reported these to be between 5 and 82% [4].

Medication adherence, specifically defined as “the extent to which a patient’s behaviour matches agreed recommendations from their health professional” [8, 13] is an essential requirement for achieving therapeutic goals. Non-adherence to treatment may vary from taking a smaller dose than prescribed to omitting a dose intermittently or taking no dose of medication [14–16]. Suboptimal adherence to rhGH treatment compromises the long-term clinical effectiveness of the treatment, leading to delayed growth response and height velocity outcomes, reduced linear growth, and a minimised final adult height, [3, 17, 18]. As rhGH treatment remains costly, non-adherence impacts substantively upon the healthcare system in terms of economic costs [11, 19].

Many theories and concepts have been developed to explain non-adherence, and recently they have been incorporated into the COM-B (capability, opportunity, motivation – behaviour) framework. This proposes that the performance of a *behaviour* is caused by a dynamic interaction amongst 3 components: *capability* (psychological or physical ability to engage and perform the behaviour, e.g., knowledge and skills), *opportunity* (physical and social environment that enables or prevents the behaviour, e.g., quality of social support), and *motivation* (reflective or automatic brain processes that either activate or inhibit the behaviour, such as beliefs, habitual processes, and emotional responses). The COM-B framework provides a comprehensive explanation of the individual drivers of adherence, which can be used to facilitate the design and development of targeted interventions [20].

The aim of this systematic review is to identify the range of potentially modifiable factors associated with treatment non-adherence amongst the paediatric GHD population. This review has built on an existing systematic review on rhGH non-adherence by Fisher and Acerini [4]. Whilst the review of Fisher and Acerini [4] included all clinical indications for rhGH treatment, the current review uniquely examines the paediatric GHD population.

Methodology

This systematic review was conducted and reported in accordance with the method outlined in the Cochrane Handbook for Systematic Reviews [21] and Preferred Re-

porting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines that evaluate healthcare interventions [22]. It is registered in the PROSPERO International Registry of Systematic Reviews (CRD-42017084238).

Search Strategy

An extensive search was undertaken of electronic databases, which included the Cochrane Library, Embase, PsycINFO, Medline, International Pharmaceutical Abstracts, Web of Science, CINAHL, and ASSIA, to identify relevant published studies. OpenGrey, EThOS, and WorldCat theses and dissertations were used to identify any relevant unpublished and grey literature. The last online search was conducted on January 8, 2018. Manual searches via journals, books chapters, and reference lists of relevant articles were also undertaken to identify any additional records. The search was limited to studies published in the English language, between 1985 and 2018. The decision to use this search period was based on the approval of recombinant human growth hormone (somatropin) by the US Food and Drug Administration (FDA) for the treatment of GHD in 1985 [23].

Search Terms

The key search terms (alternatives and synonyms) were tailored to comprise the following 4 main conceptual emphases, identified from the specific research question: (1) population-related terms, i.e. “child*” and “paediatric”/“pediatric,” (2) disease-related terms, i.e., “growth hormone deficiency,” (3) medication-related terms, i.e., “somatropin” and “injection,” and (4) adherence-related terms, i.e., “adherence,” “persistence,” and “compliance” (online suppl. Tables 1, 2; for all online suppl. material, see www.karger.com/doi/10.1159/000493211).

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria were based on the Participants, Interventions, Comparator, Outcomes and Setting (PICOS) approach in accordance with PRISMA guidelines (online suppl. Table 3).

Studies were included if they met the following criteria: (1) patients aged ≤ 18 years; (2) paediatric patients with a clinical diagnosis of GHD or parents/caregivers of paediatric patients with a diagnosis of GHD who were prescribed growth hormone treatment; (3) randomised controlled trials (RCT) and non-RCT (prospective cohort and retrospective cohort studies) or cross-sectional studies; (4) standardised measure of assessment of adherence (both validated/non-validated methods) explicitly identifiable; (5) prevalence rate of adherence/non-adherence

for GHD explicitly extractable; (6) psychosocial, clinical, or socio-demographic factors associated with adherence explicitly identifiable and measured; and (7) studies in English published between 1985 and 2018.

Data Collection and Extraction

Articles were manually screened by title and abstract to determine eligibility according to the PICOS inclusion criteria (online suppl. Table 3). Relevant full-text studies were collated and evaluated for eligibility for inclusion (online suppl. Table 4 [2, 3, 10, 12, 15, 17, 24–38]). Co-authors (V.A. and J.W.) were presented with a selection of relevant articles in order to validate the screening process; any reviewer uncertainties or disagreements were resolved by consensus. Four authors were contacted for further information and/or to retrieve access to full-text papers in which to determine eligibility. Studies that did not fulfil the criteria were omitted throughout the process, with accompanying reasons for exclusion (online suppl. Table 5 [10, 15, 24–30, 33–38]). A PRISMA flow chart outlining the full study selection process is presented in online supplementary Figure 1.

The Cochrane Consumers and Communication Review Group Data Extraction Template was used to extract data in a standardized manner, relating to the: (1) study details, (2) sample population characteristics, (3) primary outcome findings, and (4) key factor findings (online suppl. Table 6 [2, 3, 12, 17, 31, 32]). Key potentially modifiable factors were underlined and categorised according to the COM-B framework [39].

Quality Assessment

The quality of the included studies was assessed using the 14-item National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross Sectional Studies [40]. Based on the overall rating outcome across the question list, each included study was assessed to be of either “poor,” “fair,” or “good” quality. Following the initial reviewer evaluation (S.G.), 2 additional reviewers (J.W. and V.A.) independently assessed the quality and risk of bias of each study. Any discrepancies in ratings were discussed and resolved by consensus (online suppl. Table 7 [2, 3, 12, 17, 31, 32]).

Results

Study Selection Process

Twenty-one full-text articles were assessed for eligibility, of which 6 were included in this review. The full study

selection process is illustrated in online supplementary Figure 1 (full reasons for exclusion are detailed in online suppl. Table 5 [10, 15, 24–30, 33–38]).

Study Characteristics

A descriptive summary of the 6 studies included in this review is provided in online supplementary Table 8 [2, 3, 12, 17, 31, 32]. The studies were conducted in Germany [12, 31], the UK [17], the USA [2], Turkey [32], and New Zealand [3]. Included in this review were 3 retrospective observational studies [2, 17, 31], 1 prospective observational study [12], 1 longitudinal observational study [32], and 1 cross-sectional survey study [3]. The total sample size across all of the included studies was 1,369 patients (mean = 228, range = 75–724). The sample groups consisted of a range of clinical conditions, including GHD, Turner syndrome, SHOX deficiency, small for gestational age, Prader-Willi syndrome, chronic renal failure, idiopathic short stature, neurosecretory dysfunction, intra-uterine growth retardation, and bioinactive GH; the GHD patient group made up the majority in each of the 6 studies. The total sample size of GHD patients across the 6 studies was 1,206 (mean = 201, range = 48–724). The mean age of the participants across 4 studies was 11.5 years (SD = 0.93, range = 10.1–12.5). Two studies did not report the mean age of the participants: 1 study [17] reported a median age of 12.3 years and 1 study [2] gave the age ranges of children (4–12 years) and adolescents (13–17 years). Amongst 5 studies [3, 12, 17, 31, 32], 56% were male (range = 48–65); 1 study did not specify gender details [2].

Measurement of Adherence

The overall prevalence of rhGH non-adherence was found to range between 7 [32] – 71% [2]. Different methods were used to measure medication adherence (online suppl. Table 9 [2, 3, 12, 17, 31, 32]). Three studies [3, 17, 31] used issued, renewed, or redeemed rhGH prescriptions/vials as a means of measuring medication adherence and 2 studies [2, 32] used self-report questionnaires to patient and/or parents, whilst one study [12] used an electronic monitoring device in conjunction with a clinical kit software.

In the majority of studies, adherence was assessed on the basis of the number of missed injections of rhGH during a specified period. Three studies [3, 12, 31] used the following cut-offs proposed by Cutfield et al. [3]: good/high adherence, missed ≤ 1 dose per week ($\geq 85\%$ adherence); medium adherence, missed > 1 but < 3 doses per week; and poor/low adherence, missed ≥ 3 doses per week

[3]. One study [17] used slightly different categories to classify adherence, i.e., >1 injection missed per week, 1–2 injections missed per week, or >2 injections missed per week. One study [32] used the adherence criteria established by Smith et al. [10] based on the percentage of doses omitted in each evaluation period, with a classification of: 0%, excellent; 5%, good; 5–10%, fair; and >10%, poor, while another study [2] defined compliance by categorising patients into “segments” based on individual responses to potential reasons for missing doses; compliance segments were created on the basis of the number of “never” responses as follows: highly compliant, 8–9 “never” responses; occasionally non-compliant, 6–7 “never” responses; or non-compliant and skeptical, 5 or fewer “never” responses.

Quality Assessment

Five studies were rated as “good” quality [3, 12, 17, 31, 32] and 1 study was rated as “fair” [2]. Methodological issues were found within the reporting of sample size justifications, participation rates, and follow-up rates of eligible persons, the definitions of valid, reliable measures, and the minimal time frames of adherence assessment (online suppl. Table 7 [2, 3, 12, 17, 31, 32]).

Factors Associated with Adherence to rhGH Treatment

The 6 studies reported 22 different factors associated with non-adherence to rhGH treatment. An overview of the range of key potentially modifiable factors associated with paediatric non-adherence to rhGH treatment is presented in online supplementary Table 10 [2, 17, 31, 32].

Two socio-demographic factors (i.e., age [2, 12, 31] and Maori ethnicity [3]) were not categorised, as both factors were considered non-modifiable constructs and discussed separately.

Capability

Psychological Capability Factors. In 1 study, lower adherence was associated with a lack of awareness, understanding, and knowledge of the condition [2] as well as a lack of understanding of the treatment, particularly minimisation of the consequences and risks of missed rhGH doses [2]. The inability to maintain a necessary medication schedule due to forgetfulness or to maintain an adequate supply of rhGH due to the failure to renew prescriptions [32] also emerged as a key factor.

Physical Capability. Inaccurate injection technique and skill [2] of the individual responsible for rhGH administration was reported to be associated with lower

treatment adherence. Although one study found that self-administration of medication [31] compared to parental administration negatively impacted on adherence, another showed no effect [32].

Opportunity

Physical Opportunity. The discomfort or pain associated with daily injections [2] over a long duration [17, 31] was also found by several studies to be related to poor levels of adherence. Despite the increase in the choice of injection delivery devices [4, 41, 42], the association between patient choice and adherence was found to be inconsistent. Whilst one study reported that the lack of choice of injection device [17] was associated with greater non-adherence, 4 studies found that the type of injection device was not associated with adherence [2, 17, 31, 32] or with the type of rhGH product used [32]. Two studies demonstrated the negative impact of logistical difficulties on treatment adherence [17, 32]. Physical disruptions to the access of rhGH resources for patients/parents, e.g., problems with the delivery service [32] or the short duration of rhGH prescriptions given by the health-care professional (HCP) [17], were also found to be predictive factors of non-adherence.

Social Opportunity. Interpersonal influences and social cues and norms were found to influence the levels of adherence to rhGH treatment, primarily focused on the quality of the interaction between the HCP and the patient. One retrospective study showed that non-adherence was influenced by the type of HCP (hospital/non-hospital staff) providing the rhGH administration training at the initiation of treatment [17]. Inadequate contact with HCP [2] between consultations throughout the treatment pathway was also found to be associated with non-adherence. Another showed that the communicative support of the HCP within consultations [2] also played an important role in overall adherence to treatment.

Motivation

Reflective Motivation. The lack of patient/parent confidence and self-efficacy to administer the rhGH injection [31] was found by 1 study to negatively impact adherence. Two retrospective studies found that disillusionment and displeasure with the growth response and the perceived inefficacy of treatment results [2, 17] correlated with poor adherence levels. Non-acceptance of rhGH treatment [2] as a therapy for GHD, amongst patients/parents, was also found to be a key factor associated with lower adherence.

Automatic Motivation. Lifestyle disruptions and scheduling issues, e.g., being away from home [32], vacation/breaks [32], or inter-current illness [32], were identified by 1 longitudinal study as being disruptive to the established cues or stimuli for action, thereby affecting adherence.

Demographic Variables

Socio-demographic factors were not consistently related to adherence. Lower adherence was associated with increasing age (puberty/adolescence) by 3 studies [2, 12, 31], but in others no association was found with age [3, 17], gender [3], or clinical diagnosis/indication [2, 3, 12, 32]. Cultural ethnicity [3] was identified as a significant predictor but no relationship was found between rhGH adherence and either the area of residence [3] or the socio-economic status of individuals [32].

Discussion

In our review, up to 71% of GH-deficient paediatric patients were found to be non-adherent to their treatment, confirming the current adherence issue [24]. Twenty-two different factors were found to be associated with non-adherence to rhGH.

Potentially modifiable factors found to be associated with rhGH non-adherence were categorised within the COM-B framework. The factors most commonly associated with non-adherence were: the long duration of treatment [17, 31] and dissatisfaction with growth response/treatment results [2, 17]. Further key factors included: knowledge and understanding of the condition and treatment [2], discomfort and pain associated with daily injections [2], a lack of understanding of the consequences of missed rhGH doses [2], a poor administration technique [2], and forgetting to administer the medication [32], in addition to the inadequate contact with HCP and the quality of the HCP-patient relationship [2] (online Suppl. Table 10 [2, 17, 31, 32]).

Our findings concur with the wider rhGH literature, [10, 15, 24–26, 28, 29, 30, 33, 34, 36–38]. Factors unique to the wider literature included: fear of side effects/long-term complications [15, 27, 35], the preference [36] and convenience of an injection device (ease of use, technical handling, and storage) [10, 24, 36], and accessibility of the rhGH distributing pharmacy [15] as well as sociodemographic factors (more specifically, the level of parental school education) [24, 29, 34, 38].

Factors found within the current review concur with several qualitative studies which explored patient/parental views and experiences [43–45]. Patterns of self-reported reasons for non-adherence to rhGH treatment amongst these studies centred around: anxiety and fear about the needle or the pain associated with administering the injection [43–45], the lack of confidence/skill of the person administering the injection [43], ineffectiveness of treatment [43, 45], the lack of freedom to choose the injection device [44], treatment interference issues, i.e., overnight sleepovers or travel activities [43], and poor HCP/patient communication [43, 45].

While the majority of key potentially modifiable factors could be categorised directly into a single sub-component of the COM-B framework, 2 identified factors (self-administration [31] and lack of choice of the injection device [17]) were each mapped onto 2 sub-components (online Suppl. Table 10 [2, 17, 31, 32]). The effect of “self-administration” on adherence could be explained by the practical ability of administering an injection (physical capability) as well as by the confidence and self-efficacy of the individual to administer the injection (reflective motivation). Similarly, the effect of the lack of choice of injection device on adherence could be defined by the physical absence of injection devices (physical opportunity), with the device being chosen on behalf of the patient by the HCP. Alternatively, the lack of ownership over their treatment due to the lack of injection device choice could, in turn, influence the patients’/caregivers’ beliefs about their condition or treatment (reflective motivation).

Whilst 3 studies found an association between rhGH adherence and age [2, 12, 31], 2 did not [3, 17]. Similarly, in 1 study it was found that self-administration of medication [31] compared to parental administration negatively impacted on adherence to treatment, yet in another study no association was found between the person who administered the injection [32] and rhGH adherence. It is uncertain whether the conflicting evidence is a result of heterogeneity between studies, the difference in methods and definitions used across studies, or the various sample sizes and populations being assessed.

Limitations

Amongst the included studies, there was a variety of methods used to measure adherence, each with its own advantages and disadvantages [46]; these included: self-report questionnaires; issued, renewed, or redeemed prescriptions/vials; and electronic monitors. The variability amongst measures may explain some of the disparity

found in reported adherence rates. Interestingly, a definitive pattern between the prevalence rate of adherence and the method employed for measurement was not identified. A large dissimilarity of prevalence was found across studies using subjective methods as a means to assess adherence (i.e., 7% [32] and 71% [2]). Similarly, amongst studies using objective measures, the prevalence of non-adherence was also found to be relatively inconsistent (e.g., studies using issued, renewed, or redeemed rhGH prescriptions/vials reported rates of 62 [17], 66 [3], and 24% [31]), and the single study using the electronic device in conjunction with clinical kit software reported the lowest non-adherence rate (i.e., 22.9%) [12].

The range of adherence measures, in addition to the varied cut-off thresholds for adherence and the differing terminology used to define these threshold points – e.g., “excellent” to “poor” [32] versus “highly compliant,” “occasionally non-compliant,” and “non-compliant and skeptical” [2] – consequently made synthesis of the study results and drawing of definitive, comparative conclusions challenging.

The aim of the current review was to examine the paediatric GHD population exclusively with regard to the prevalence rate of treatment non-adherence and associated factors. The prevalence rate for the GHD sample group was able to be unequivocally extracted in each of the included studies. However, as the studies had not distinguished the factors associated with treatment non-adherence per condition group, this was not able to be achieved in this review, although notably in the included studies the GHD population accounted for the majority of each sample group prescribed growth hormone treatment.

Recommendations for Future Research

To facilitate meaningful interpretations and comparisons across studies, a more strategic and coordinated methodological approach is essential [47]. The heterogeneous nature of studies presents a continual challenge for research and clinical practice. It is therefore recommended that, where possible, researchers work toward a level of standardisation across adherence measurement and definitions. The emergence of new electronic delivery devices (e.g., the easypod®) in recent years could facilitate this advancement.

Conclusion

This review highlights the scope of the adherence problem evident amongst the paediatric GHD population and in addition presents the wide range of potentially modifiable factors that explain this health-related behaviour. Informed with the findings of the review, it is essential that future research begin to focus on designing, developing, and implementing new, targeted, and evidence-based intervention strategies with the purpose of optimising treatment adherence, supporting clinical practice, and improving clinical health outcomes.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflict of interests to declare.

References

- 1 Acerini C, Albanese A, Casey A, Denvir L, Jones J, Mathew V, et al. Initiating growth hormone therapy for children and adolescents. *Br J Nurs*. 2012 Oct;21(18):1091–7.
- 2 Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract*. 2008 Mar;14(2):143–54. Available from: <https://doi.org/10.4158/EP.14.2.143>.
- 3 Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS One*. 2011 Jan;6(1):e16223.
- 4 Fisher BG, Acerini CL. Understanding the growth hormone therapy adherence paradigm: a systematic review. *Horm Res Paediatr*. 2013;79(4):189–96.
- 5 Polak M, Blair J, Kotnik P, Pournara E, Pedersen BT, Rohrer TR. Early growth hormone treatment start in childhood growth hormone deficiency improves near adult height: analysis from NordiNet® International Outcome Study. *Eur J Endocrinol*. 2017 Nov;177(5):421–9.
- 6 Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. *J Clin Endocrinol Metab*. 2006 Jun;91(6):2047–54.
- 7 Haverkamp F, Gasteyger C. A review of biopsychosocial strategies to prevent and overcome early-recognized poor adherence in growth hormone therapy of children. *J Med Econ*. 2011;14(4):448–57.
- 8 Horne R [Internet]. Compliance, Adherence, and Concordance: Implications for Asthma Treatment. Available from: [http://journal.chestnet.org/article/S0012-3692\(15\)32958-5/abstract](http://journal.chestnet.org/article/S0012-3692(15)32958-5/abstract).
- 9 Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al.; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012 May;73(5):691–705.

- 10 Smith SL, Hindmarsh PC, Brook CG. Compliance with growth hormone treatment—are they getting it? *Arch Dis Child*. 1993 Jan;68(1):91–3. Available from: <https://doi.org/10.1136/ADC.68.1.91>.
- 11 Haverkamp F, Johansson L, Dumas H, Langham S, Tauber M, Veimo D, Chiarelli F. Observations of nonadherence to recombinant human growth hormone therapy in clinical practice. *Clin Ther*. 2008;30(2):307–16.
- 12 Hartmann K, Ittner J, Müller-Rossberg E, Schönau E, Stephan R, Ullrich KP, et al. Growth hormone treatment adherence in prepubertal and pubertal children with different growth disorders. *Horm Res Paediatr*. 2013;80(1):1–5.
- 13 National Institutes for Health and Care Excellence [Internet]. Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence. Available from: <https://www.nice.org.uk/guidance/cg76>.
- 14 Norgren S [Internet]. Adherence Remains a Challenge for Patients Receiving Growth Hormone Therapy. Available from: <http://europepmc.org/abstract/med/19550391>.
- 15 Mohseni S, Heydari Z, Qorbani M, Radfar M. Adherence to growth hormone therapy in children and its potential barriers. *J Pediatr Endocrinol Metab*. 2018 Jan;31(1):13–20.
- 16 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005 Aug;353(5):487–97.
- 17 Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, Ong KK, et al. Monitoring of concordance in growth hormone therapy. *Arch Dis Child*. 2008 Feb;93(2):147–8.
- 18 Desrosiers P, O'Brien F [Internet]. Patient Outcomes in the GHMonitor: The Effect of Delivery Device on Compliance and Growth. Available from: <http://europepmc.org/abstract/med/16456500>.
- 19 Kirk J. Indications for growth hormone therapy in children. *Arch Dis Child*. 2012 Jan;97(1):63–8.
- 20 Jackson C, Eliasson L, Barber N, Weinman J. Applying COM-B to medication adherence. *Eur Health Psychol*. 2014;16(1):7–17.
- 21 Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: Wiley;2008.
- 22 Liberati A, Altman D [Internet]. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies that Evaluate Health Care Interventions: Explanation and Elaboration. Available from: <http://annals.org/article.aspx?articleid=744698>.
- 23 National Institute for Health and Care Excellence [Internet]. Human Growth Hormone (Somatropin) for the Treatment of Growth Failure in Children. Available from: <https://www.nice.org.uk/guidance/ta188>.
- 24 Bagnasco F, Di Iorgi N, Roveda A, Gallizia A, Haupt R, Maghnie M; Adherence Investigators Group *. Prevalence and correlates of adherence in children and adolescents treated with growth hormone: a multicenter Italian study. *Endocr Pract*. 2017 Aug;23(8):929–41.
- 25 Ergur AT, Gunes SO, Bahceci O. The adherence to growth hormone therapy in children with growth hormone deficiency. *Horm Res Paediatr*. 2017;88(1):311.
- 26 Farfel A, Shalitin S, Koren-Morag N [Internet]. Long-Term Adherence to Growth Hormone Therapy in a Large Health Maintenance Organization Cohort. Available from: <https://www.karger.com/Article/Pdf/481424>.
- 27 Sayarifard F, Imchek FB, Badri S, Faghihi T, Qorbani M, Radfar M. Growth Hormone Utilization Review in a Pediatric Primary Care Setting. *J Res Pharm Pract*. 2017 Jan-Mar;6(1):40–3.
- 28 Hughes IP, Harris M, Choong CS, Ambler G, Cutfield W, Hofman P; Australasian Paediatric Endocrine Group. Growth hormone regimens in Australia: analysis of the first 3 years of treatment for idiopathic growth hormone deficiency and idiopathic short stature. *Clin Endocrinol*. 2012;77(1):62–71.
- 29 De Pedro S, Murillo M, Salinas I, Granada ML, Martinez M, Puig-Domingo M, et al. Variability in adherence to rhGH treatment: socioeconomic causes and effect on children's growth. *Growth Horm IGF Res*. 2016 Feb;26:32–5.
- 30 Kremidas D, Wisniewski T, Divino VM, Bala K, Olsen M, Germak J, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. *J Pediatr Nurs*. 2013 Jan;28(1):55–63.
- 31 Lass N, Reinehr T. Low Treatment Adherence in Pubertal Children Treated with Thyroxine or Growth Hormone. *Horm Res Paediatr*. 2015;84(4):240–7.
- 32 Aydın BK, Aycan Z, Şıklar Z, Berberoğlu M, Öcal G, Çetinkaya S, et al. Adherence to growth hormone therapy: results of a multicenter study. *Endocr Pract*. 2014 Jan;20(1):46–51.
- 33 Bozzola M, Pagani S, Iughetti L, Maffei C, Bozzola E, Meazza C. Adherence to growth hormone therapy: a practical approach. *Horm Res Paediatr*. 2014;81(5):331–5.
- 34 Drosatou C, Karachaliou F, Vlachopapadopoulou EA, Petrou V, Kaloumenou E, Michalakos S [Internet]. Assessment of Compliance with GH Therapy. Available from: <http://abstracts.eurospe.org/hrp/0082/hrp0082p3-d1-818.htm>.
- 35 Miller BS, Rotenstein D, Deeb LC, Germak J, Wisniewski T. Persistence with growth hormone therapy in pediatric patients. *Am J Pharm Benefits*. 2014;6(1).
- 36 Oyarzabal M, Aliaga M, Chueca M, Echarte G, Ulied A. Multicentre survey on compliance with growth hormone therapy: what can be improved? *Acta Paediatr*. 1992 Apr;87(4):387–91.
- 37 Leiber E, Pilpel D, Carel CA, Levi E, Zaidik Z. Coping and satisfaction with growth hormone treatment among short-stature children. *Horm Res*. 1993;40(4):128–35.
- 38 Gács G, Hosszu E. The effect of socio-economic conditions on the time of diagnosis and compliance during treatment in growth hormone deficiency. *Acta Paediatr Hung*. 1991;31(2):215–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1867888>.
- 39 Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. 2011 Apr;6(1):42.
- 40 National Heart, Lung, and Blood Institute [Internet]. National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross Sectional Studies. Available from: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.
- 41 Dumas H, Panayiotopoulos P, Parker D, Pongpaichana V. Understanding and meeting the needs of those using growth hormone injection devices. *BMC Endocr Disord*. 2006 Oct;6(1):5.
- 42 Ahmed SF, Smith WA, Blamires C. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis. *Arch Dis Child*. 2008 Feb;93(2):110–4.
- 43 Brod M, Højbjørre L, Alolga SL, Beck JF, Wilkinson L, Rasmussen MH [Internet]. Understanding Treatment Burden for Children Treated for Growth Hormone Deficiency. Available from: <https://doi.org/10.1007/s40271-017-0237-9>.
- 44 van Dongen N, Kaptein A. Parents' views on growth hormone treatment for their children: psychosocial issues. *Patient Prefer Adherence*. 2012;6:547–53.
- 45 Marini MG, Chesi P, Mazzanti L, Guazzarotti L, Toni TD, Salerno MC, Sacchetti C. Stories of experiences of care for growth hormone deficiency: the CRESCERE project. *Future Sci OA*. 2016;2(1):FSO82.
- 46 Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. *BMC Med Res Methodol*. 2011 Nov;11(1):149.
- 47 McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA*. 2002 Dec;288(22):2868–79. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12472329>.