

Evaluation of final height prediction and selected parameters in Polish patients with severe and partial growth hormone deficiency

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Submitted: 2014-05-27 *Accepted:* 2014-06-12 *Published online:* 2014-06-27

Key words: **severe growth hormone deficiency; partial growth hormone deficiency; target height; predicted adult height; final height**

Neuroendocrinol Lett 2014; **35**(3):242–247 PMID: 24977976 NEL350314A07 © 2014 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: The main goal of growth hormone therapy is to reach the height in the population ranges. The aim of the study was the comparison of selected methods for predicting final height in Polish patients with severe (sGHD) and partial (pGHD) growth hormone deficiency. **METHODS:** 149 children with growth hormone deficiency treated with rhGH in the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology Developmental Age, PUM, in Szczecin, in 2000–2010 have been evaluated. Patient were divided into two groups: sGHD and pGHD. Two methods of final height prediction have been used: Roche-Weiner-Thissen (RWT) and target height (TH), results were compared to the final height (FH). 117 children finished therapy in the analysed period and reached final height. **RESULTS:** The mean FH was similar in both groups. There was no significant difference between the accuracy of prediction methods of TH and RWT between groups of pGHD v. sGHD. Further analysis revealed, that in the group of boys with sGHD the prediction error of RWT was significantly lower than of the TH method ($p < 0.05$). **CONCLUSIONS:** It seems that in the group of boys with sGHD RWT is a more accurate method than TH.

Abbreviations:

BMI - Body Mass Index
BP - Bayley-Pinneau
errP - Prediction Error
FH - Final Height
GH - Growth Hormone
GHD - Growth Hormone Deficiency
HSD - Height Standard Deviation
IGF-1 - Insulin-like Growth Factor

IGF-BP3 - Insulin-like Growth Factor Binding Protein 3
MPH - Mean Parental Height
PAH - Predicted Adult Height
pGHD - Partial Growth Hormone Deficiency
rhGH - Recombinant Human Growth Hormone
RWT - Roche-Weiner-Thissen
SD - Standard Deviation
sGHD - Severe Growth Hormone Deficiency
TH - Target Height

INTRODUCTION

Short stature is most often defined as height under 3rd percentile in reference charts for given age, gender and population (Nicol *et al.* 2010). Growth hormone deficiency (GHD) is estimated at 1:3 000 to 1:15 000 cases (Kumaran & Dattani 2008; Lindsay *et al.* 1994; Romer & Walczak 2009). Diagnosing of GHD is based on an analysis of various data: family history, auxological parameters, bone age, IGF-I, IGFBP-3 concentration and GH secretion (Tenenbaum-Rakover 2008; Growth Hormone Research Society 2000; Waldman & Chia 2013). GHD is treated with recombinant human growth hormone (rhGH) mainly in children but also (in some countries) in adults with severe GHD. One of the main purposes of rhGH therapy in children is to achieve adult height within population range. At the beginning of the therapy an adult height assessment is performed. The easiest method is to calculate height by the modified Tanner method – target height (TH). More complex ones include Roche-Weiner-Thissen (RWT) and Bayley-Pinneau (BP) etc. (Roemmich 1997; Styne 2004). In recent years new mathematic models of adult height prediction are created (Wit *et al.* 2013).

MATERIAL AND METHODS

Medical records of 149 children (103 boys and 46 girls) from the Western Pomerania Region treated with rhGH in Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology Developmental Age, Pomeranian Medical University, in Szczecin between 1 Jan 2000 and 30 Sep 2010 were analysed. All patients were qualified for the therapy according to agreed criteria: height below $-2SD$, impaired growth velocity (age and sex matched), 2 and more years of bone age delay, growth hormone peak below 10 ng/ml in two stimulation test (Romer *et al.* 2002). Children with chronic illnesses were excluded. The mean age of the patients at the beginning of the treatment was 12.9 ± 2.7 years. The mean parental height was $\bar{x} = -1.0 \pm 0.9 SD$.

The pubertal development of children was estimated according to Tanner staging: 78 (52.3%) children presented with stage 1, 59 (39.6%) with stage 2 and 12 (8.1%) with stage 3.

The height measurement was taken with Harpenden-type stadiometer and calculated as height standard deviation (HSD). Weight was measured using a medical scale, the body mass index (BMI) was calculated and expressed as standard deviation based on Polish population charts (Palczewska & Niedźwiecka 2001). Bone age assessment according to the Greulich-Pyle's Atlas (Greulich & Pyle 1993). GH secretion stimulating tests with Clonidine and L-DOPA were performed (Ginalska-Malinowska & Malinowska 2009). Based on the results the severe GHD group (sGHD – peak GH under 5 ng/ml in both tests) and the partial GHD group (pGHD – peak GH between 5 and 10 ng/ml, never

reaching the value of 10 ng/ml) were formed. The sGHD group consisted of 73 (49%) children (50 boys) while there were 76 (51%) children with pGHD (53 boys).

According to performed magnetic resonance imaging idiopathic growth hormone deficiency was noted in 131 (87.9%) patients. Other pituitary hormones were investigated. Isolated growth hormone deficiency was revealed in 136 (91.3%) children.

The patients' adult heights were calculated using the modified parent height equation (TH):

for boys: $TH = MPH + 6.5$ cm,

for girls: $TH = MPH - 6.5$ cm (Ranke & Lindberg 2009; Tanner 1970),

and the modified Roche-Weiner-Thissen (RWT) equation (Styne 2004):

1. the length in a lying position (cm)
(if standing 1.25 cm was added) \times variable*
+
2. body weight (kg) \times variable*
+
3. mean parental height (cm) \times variable*
+
4. bone age (years) \times variable*
+
5. the correct ratio for the age group*
=

height prediction (cm).

* multipliers by tables of Styne (2004).

The treatment was continued until one of the end points was achieved: epiphyseal closure or growth velocity below 3 cm/year (Romer *et al.* 2002). 117 (78.5%) children: 62 (43 boys and 19 girls) with pGHD and 55 (37 boys and 18 girls) of sGHD finished the treatment and reached final height. Patients were treated for 4.3 ± 2.1 years.

Auxological parameters were checked after cessation of the therapy. The expected height calculated by both methods was compared to the final height achieved (FH). Prediction error (errP) was calculated using equations: $errP(TH) = TH - FH$ and $errP(RWT) = RWT - FH$. The results were compared.

The average dose of rhGH was 0.031 mg/kg/day, injected every evening, subcutaneously. The mean interruption in the therapy lasted 1 week.

Basics statistics (mean \pm SD, median, amount and frequency of occurrence), the Kolmogorow-Smirnow test, the t-Student and Mann-Whiney tests, the variation analysis test (ANOVA), co-variation analysis test (ANCOVA) or the Kruskal-Wallis tests, the χ^2 Pearson test, Fisher test were used. As statistically significant differences the probability $p < 0.05$ was taken. All done with the STATA 11 program.

The study was reported to the Pomeranian Medical University Bioethics Committee, however due to its retrospective character, it did not require the Committee's approval.

Tab. 1. Data regarding the height predicted using both methods and height achieved, the comparison between the severe (sGHD) and the partial GH (pGHD) deficiency groups.

Variable	pGHD (n=62)	sGHD (n=55)	p-value
FH [SD]	-1.6±1.1	-1.4±1.2	ns
TH [SD]	-1.1±0.7	-1.0±0.8	ns
RWT [SD]	-1.1±1.0	-1.4±1.1	ns

FH - final height, TH - target height, PAH - predicted adult height (RWT), SD - standard deviation, pGHD - partial growth hormone deficiency, sGHD severe growth hormone deficiency, *p* - statistical relevance level, ns - non-significant

RESULTS

In the study group the mean age at the beginning of the treatment was 12.9±2.7 years. No significant differences of age were noted between the pGHD and sGHD groups. The mean height in the study group was -3.3±0.9SD, bone age delay 2.4±1.4SD. There were no significant differences of auxological parameters but BMI (pGHD -1.0±1.2SD vs sGHD 0.1±2.0SD; *p*<0.001) between these groups.

No statistically significant differences of growth velocity (GV) in the first year of treatment were found between these both groups.

At the end of the treatment the mean age did not differ between the groups. The mean final height was -1.5±1.0SD (improvement by 1.8±1.1SD; *p*<0.001). FH, TH and RWT did not differ between the groups (Table 1).

In both groups the methods of predicting final height (TH and RWT) were analysed. Children of sGHD and pGHD groups achieved significantly lower FH than predicted using the TH method (in both groups *p*<0.05) (Table 1). No statistically significant differences in errP(TH) were found between these groups. A gender-based analysis were performed. At sGHD girls no significant difference was found between FH and TH. sGHD boys were shorter FH -1.6±1.2SD comparing to TH -1.0±0.8SD (*p*<0.05); errP(TH) was 0.6±1.3SD. Among pGHD girls no statistically significant difference was found between FH and TH. Boys with pGHD were shorter: FH -1.6±1.1SD compared to TH -1.2±0.8SD (*p*<0.05); errP(TH) was 0.4±1.1SD.

Predicted final height calculated with the RWT method did not differ statistically between the sGHD and pGHD group (Table 1). The height predicted for the analysed group using the RWT method was significantly higher than FH (*p*<0.05). In the sGHD group FH did not differ significantly from the PAH, even if gender was taken into account. FH in the pGHD group was, however, statistically lower than PAH (*p*<0.05). The prediction error of the RWT method in the pGHD group was 0.5±1.1SD. A gender-based analysis of the partial GH deficiency group was performed. The height

achieved by girls of the pGHD group was significantly lower than previewed, -1.7±1.0SD vs -1.0±0.8SD respectively (*p*<0.05). Among the boys of the pGHD group, the achieved height did not differ statistically from the PAH; respectively -1.6±1.1SD vs -1.3±0.9SD.

The results achieved by both methods were then compared. It was noted that the prediction errors did not differ between these two methods. errP was checked for both genders. Based on errP for the group of girls, no method was deemed superior to other. For the boys' group however, it was concluded that the RWT method carries a substantially lower risk of error than TH (*p*<0.05). Groups of severity of GHD were also compared. It was concluded, that in the sGHD group, PAH calculated using the RWT method was statistically lower than TH (*p*<0.05). No similar difference was found in the pGHD group. In sGHD group FH did not differ significantly by RWT method. While the difference between TH and FH was significant (*p*<0.05). Height predicted using both methods, compared to FH in both the severe and the partial GH deficiency groups is presented on Figure 1.

Neither in the sGHD, nor in the pGHD group did the RWT method error differ in a statistically significant way, compared to the TH. Further sGHD and pGHD group analysis included gender. In the partial GHD group, the errors of both methods did not differ significantly between the boys and the girls. In the sGHD boys however, predicting final height using the RWT method resulted in a smaller error compared to the TH, respectively 0.1±1.3SD vs. -0.6±1.3SD (*p*<0.05). In sGHD girls both methods were equal (Figure 2).

DISCUSSION

The study comprised 149 Polish children of Western Pomeranian Region of Poland inhabited by 2 million people. As Polish population is homogenous we tried to match obtained data, as much as it was possible, with other Polish studies' results. 49% of patients presented sGHD and 51% pGHD. Boys dominated in both subgroups. These numbers resemble those published by Kostecka & Wąsikowa (2005). In other studies sGHD was noted in a noticeably smaller percentage of patients from 22 to 26% and all those groups were preponderantly male (Hilczer *et al.* 2005; Mysiek-Prucnal *et al.* 2010; Tauber *et al.* 1997). The average age at the beginning of the therapy was 12.9±2.7 years. The late onset of treatment resulted from delays in referring to specialists. Tauber *et al.* (1997) described patients of similar age. In a study by Kędzia *et al.* (2005) and Petriczko *et al.* (2009) the treatment began later. However, in other studies the age was lower 10.3 to 11.8 years (Korpala-Szczyrska & Balcerska 2008; Korpala-Szczyrska *et al.* 2006; Witkowska-Sędek *et al.* 2009). It is known, that the late age at the beginning of therapy results in its shorter duration. A world-wide tendency can be observed to begin therapy as early as possible, usually below 9y/0

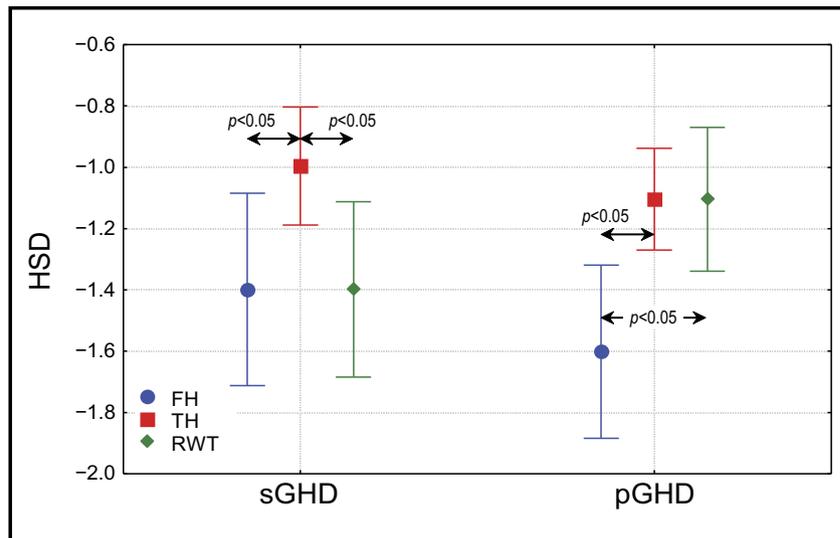


Fig. 1. Height predicted using both methods, compared to the height achieved (expressed in standard deviation) in both the severe and the partial GH deficiency groups. HSD - height standard deviation, FH - final height, TH - target height, RWT - predicted adult height.

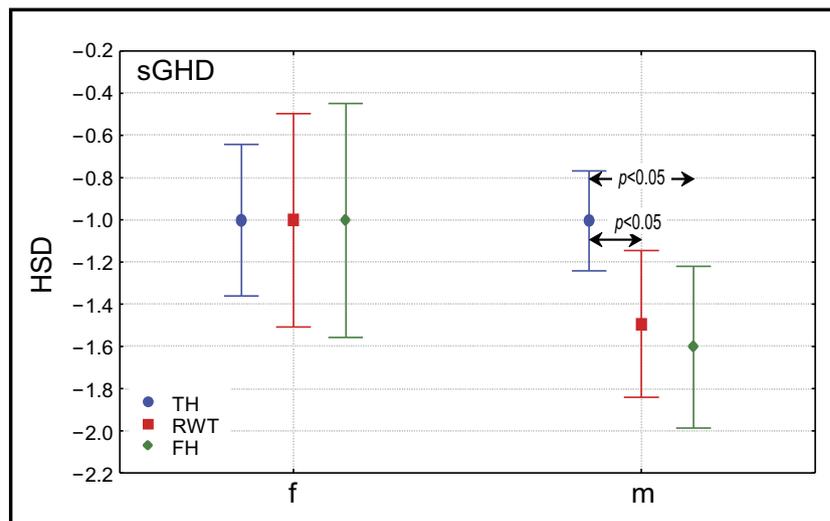


Fig. 2. Height predicted using both methods, compared to the height achieved (expressed in standard deviation) in boys and girls of the severe GH deficiency group. HSD - height standard deviation, FH - final height, TH - target height, RWT - predicted adult height, f - girls, m - boys.

(Clayton *et al.* 2007; Cole *et al.* 2004). Both in these and in the Hilczer *et al.* (2005) studies no statistically significant difference of age were found between pGHD and sGHD groups. Children's height at the beginning of the treatment did not differ statistically between the pGHD and sGHD groups, in Hilczer *et al.* (2005) study alike. In two other studies it was concluded, that children of the sGHD group were shorter, when compared to the pGHD group (Coutant *et al.* 2001; Smyczyńska *et al.* 2007). The mean growth velocity in the first year of rhGH treatment also did not differ statistically between sGHD and pGHD. That was similar to other analysed groups (Mysłek-Prucnal *et al.* 2010; Hilczer *et al.* 2006).

Mean FH after cessation of the treatment did not differ statistically between the sGHD and pGHD

groups. Similar observations have been made by Mysłek-Prucnal *et al.* (Mysłek-Prucnal *et al.* 2010). In Hilczer's *et al.* (2005) study children from the sGHD group achieved a significantly higher height that those from the pGHD group.

One of the challenges concerning patients with growth hormone deficiency is estimating their adult height. In this study two estimation methods were used: TH and RWT. TH is a commonly used method, due to its simplicity. RWT is far more time-consuming and present rather in scientific studies, than in clinical practice. We checked the prediction values of these two methods for GHD children.

Target height (TH) did not differ significantly between the groups of sGHD and pGHD. Similarly

in the study by Smyczyńska *et al.* (2007) in all groups however, the TH was higher and equaling 0.7SD for the sGHD group and $-0.6SD$ for the pGHD group. In Hilczer *et al.* (2005) study TH calculated for the sGHD group was significantly higher than in the pGHD group. In our study children from both groups achieved significantly lower FH than predicted with TH method. No statistically significant differences of the prediction errors between those groups were found. In the study by Hilczer *et al.* (2005), the patients from both groups did not achieve TH, although the difference in the sGHD group was greater than in pGHD. A gender sub-analysis was performed. Among sGHD and pGHD girls no significant difference between FH and TH was found. In both groups of boys the TH was overestimated compared to FH ($p < 0.05$).

PAH (RWT) calculated for our group did not differ statistically between the sGHD and pGHD groups. Interestingly, in our study group, the FH of children with sGHD did not differ from PAH(RWT) in a statistically significant way, even gender-considered. Children from the pGHD group did not, however, achieve their PAH. A gender-based analysis proved that FH in the group of boys with pGHD did not differ significantly from PAH. In the group of girls with pGHD though, FH was significantly lower than prognosed by RWT. Based on the foregoing results it appears that the RWT method is accurate in calculating PAH for the whole sGHD group and for the boys with pGHD. No similar studies have been found in literature.

A comparison of the height prediction methods was done to assess, whether any of them is superior to other. The prediction errors of both methods in the study group did not differ significantly. The gender analysis revealed that in the group of girls no method was superior. Therefore, it appears that the simple TH method is sufficiently accurate to predict the height of girls. In the group of boys the error of RWT method was lower than TH. So for the boys, it could be recommended to use the more complex RWT method. In order to potentially specify a smaller and more defined group of patients, who would benefit from this time-consuming method, a sub-group analysis was performed on the basis of the severity of GHD. ErrP(RWT) compared to errP(TH) did not differ significantly between the sGHD and pGHD groups. After also taking gender into consideration. It was, however, concluded, that in the sGHD-boys group the RWT method carried a significantly smaller prediction error than the TH. In the remaining groups, i.e. the boys and girls with pGHD, none method proved better than the other. It appears therefore, that knowing the initial GH deficiency level of a group of boys, the RWT method should be used to predict the height of those with sGHD. In the remaining sub-groups, both methods appear equally accurate. It is interesting, why despite analysing a large number of variables the RWT method does not excel in all groups. Roemmich *et al.* (1997) suggest, that problems with

the accuracy of the prediction methods, which include bone age, might origin from miscalculations in assessing the bone age itself. Zachmann *et al.* (1978), on the other hand, attributes it to an earlier onset of puberty in children included in the studies, than at the time when these prediction methods were created.

To sum up, it seems that RWT method is superior to TH in group of boys with sGHD.

CONCLUSIONS

In the group of boys with sGHD the RWT method carries a substantially lower risk of error than TH method and may be considered superior when calculating PAH.

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