ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2023.2022-12-18

J Clin Res Pediatr Endocrinol 2023;15(3):268-275

Growth Hormone Dosing Estimations Based on Body Weight Versus Body Surface Area

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What is already known on this topic?

Drug doses calculated based on body weight and body surface area may be different under certain circumstances.

What this study adds?

In children younger than 11 years of age with body mass index levels less than 18 kg/m^2, growth hormone dosing based on body weight may be preferable.

Abstract

Objective: Both body weight (BW)- and body surface area (BSA)-based dosing regimens have been recommended for growth hormone (rhGH) replacement. The aim was to compare the two regimens to determine if either resulted in inadequate treatment depending on anthropometric factors.

Methods: The retrospective study included children diagnosed with idiopathic isolated growth hormone deficiency. BW-based dosing in mcg/kg/day was converted to BSA in mg/m^2/day to determine the equivalent amounts of the given rhGH. Those with a BW-to-BSA ratio of more than 1 were allocated to the "relatively over-dosed group", while the remaining patients with a ratio of less than 1 were assigned to the "relatively under-dosed" group. Patients with a height gain greater than 0.5 standard deviation score (SDS) at the end of one year were classified as the height gain at goal (HAG), whereas those with a height gain of less than 0.5 SDS were assigned as the height gain not at goal (NHAG).

Results: The study included 60 patients (18 girls, 30%). Thirty-six (60%) patients were classified as HAG. The ratio of dosing based on BW-to-BSA was positively correlated both with the ages and body mass index (BMI) levels of the patients, leveling off at the age of 11 at a BMI of 18 kg/m^2. The relative dose estimations (over- and under-dosed groups) differed significantly between the patients classified as HAG or NHAG. Fifty-six percent of NHAG compared to 44% of HAG patients received relatively higher doses, while 79% of HAG compared to 21% of NHAG received relatively lower doses ($p = 0.006$). When the patients were subdivided according to their pubertal status, higher doses were administrated mostly to the pubertal patients in both the NHAG and HAG groups. In the pre-pubertal age group, 73% of NHAG compared to 27% of HAG received relatively higher doses, while 25% of NHAG compared to 75% of HAG received relatively lower doses ($p = 0.01$).

Conclusion: Dosing based on BW may be preferable in both prepubertal and pubertal children who do not show adequate growth responses. In prepubertal children, relatively lower doses calculated based on BW rather than BSA provide similar efficacy at lower costs.

Keywords: Body surface area, body weight, growth hormone, IGF-1, IGFBP-3, pharmacotherapy

Introduction

Dysfunction of the growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis may result in varying degrees of growth failure and a variety of other pathological clinical features, including central obesity, loss of lean muscle mass, osteoporosis, deterioration of metabolic profile, and decreased cardiac function (1,2,3). The diagnosis of growth

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Conflict of interest: None declared
Received: 28.12.2022
Accepted: 27.03.2023

hormone deficiency (GHD) is accomplished by combining medical history, auxological measures, biochemical markers, and radiological imaging (2,4).

The standard treatment for GHD is recombinant human growth hormone (rhGH) replacement, which is customized to each child's body weight (BW) or body surface area (BSA) (5). Both BSA- and BW-based dose regimens have been recommended for rhGH replacement, on the assumption that they are equally effective (5,6). Yet, some countries still choose one regimen over the other (7,8,9,10,11).

Nevertheless, under certain circumstances, the differences between the two dosing regimens may become apparent (4,7,8,12). For instance, it has been demonstrated that BW-based dosing considerably underestimates the necessary treatment in individuals with weights of less than 30 kg (6). In contrast, due to disparities in drug clearance, obese patients are at risk of over-exposure when BW-based dosing is used, and of underexposure when BSA-based dosing is preferred (13). Hence, alternate rhGH dosing may be utilized for certain patient groups to boost effectiveness and/or to decrease toxicity (13,14).

In general, BSA-based regimens are favored for antineoplastic medications, whereas BW-based regimens are favored for cardiovascular, central nervous system, and anti-infective treatments (13). BSA-based dosing has been considered to be more closely associated with total body water, extracellular body fluid, total clearance, liver volume, and renal function (15,16). Given that rhGH is predominantly metabolized in the liver and kidneys, and the kidneys account for around 60-90% of the clearance, BSA-based dosing seems to be a more favorable method for rhGH replacement (7,17,18). However, there is insufficient data to support one over the other (5).

There is limited data (7,8) comparing the effectiveness of different rhGH dosages with regard to BSA versus BW. Homogenous studies on BW and BSA-based dosing strategies are needed. This retrospective study was designed to compare the rhGH doses in BW versus BSA in children diagnosed with idiopathic isolated GH deficiency (IGHD) who were not obese. Moreover, based on the growth responses of the patients over the first year of treatment, it would be evaluated whether either of the two regimens would result in higher or lower treatment under different conditions of age and patient anthropomorphic characteristics.

Methods

Patients

The retrospective study included children aged 1-18 years from two different centers. Individuals with obesity, defined as a body mass index (BMI) standard deviation (SD) scores ≥2, genetic anomalies, scoliosis, chronic diseases, such as diabetes mellitus or celiac disease, a history of significant trauma, low birth weight, neoplasia, brain tumor, or intracranial radiation were excluded from the study. Children with short stature who had IGHD and were treated with rhGH for at least one year between 2017 and 2022 were included. GHD was suspected in the presence of short stature (< -2 SDS) or growth deceleration (velocity < 25% of corresponding chronological age), and diagnosed when serum peak GH concentration was less than 7 ng/mL in two different GH stimulation tests (clonidine, insulin tolerance test, and levodopa) (2,9). Isolated deficiency is defined as the presence of a solitary pituitary hormone deficiency. Each child received 25-35 mcg/kg/day of rhGH replacement (4). The changes in height velocity and height SD scores were evaluated to assess treatment efficacy while IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels were monitored in order to avoid excessive dosing to ensure safety of the treatment (2,4,19,20). Clinical and laboratory data were monitored every 6-12 months to adjust rhGH doses (mg) (2,4). To exclude concomitant pathologies, each patient underwent pituitary MRI at the start of the therapy.

Data Collection

The following clinical parameters were recorded: age (years); gender; pubertal status [according to Tanner and Whitehouse (21)]; bone age [calculated according to the Greulich and Pyle (22) Atlas; height [measured with a sensitivity of 0.1 cm, using a Harpenden stadiometer, (cm)], weight [measured using a scale with a sensitivity of 0.1 kg, (kg)], BMI (kg/m^2), target height (mother's height + father's height)/2 ± 6.5, (cm)], predicted adult height [calculated according to the Roche et al. (23) method, (cm)], and the respective SD scores [calculated according to Turkish standards (24)]. The IGF-1/IGFBP-3 levels and the respective SD scores were recorded (24). The prescribed rhGH doses based on BW were also recorded. All data, which was re-evaluated every six months, was recorded.

Design of the Study

For the purpose of this paper, BW-based dosing in mcg/kg/day, which is routinely employed in our clinical practice, was converted to BSA in mg/m^2/day. Assuming that the average BW of a child with a BSA of 1 m^2 is 28 kg (7,8), all doses were separately converted to equivalent BSA formats. Hence, the routinely prescribed doses of 25, 30, and 35 mcg/kg/day were found to be equivalent to 0.7, 0.8, and 1 mg/m^2/day, respectively.

Then the BSA of each patient was calculated separately using the following empirical formulas:

i. Costeff's Formula (25): BSA (m^2) $= \frac{4\,x\,weight\,(kg) + 7}{weight\,(kg) + 90}$

ii. Mosteller's Formula (26): BSA (m^2) $= \sqrt{\frac{(weight\,(kg) \times height\,(cm))}{3600}}$

Finally, initially prescribed doses based on BW (mcg/kg/day) and the hypothetically calculated equivalent doses based on BSA (mg/m^2/day) were calculated for each patient to be given as milligrams per day (mg/day).

Stratification of the Patients

Patients were divided into two groups based on their height increase over one year. The change in height SD score was determined by subtracting the height SD score measured at the beginning of treatment from the height SD score measured after the first year of rhGH treatment. Based on Bang criteria (27), those with a height gain greater than 0.5 SD score at the end of one year were classified as height gain at goal (HAG), whereas those with a height gain of less than 0.5 SD score were classified as height gain not at goal (NHAG).

Patients were also divided into two groups based on their actual (BW-based) and estimated (BSA-based) rhGH doses in mg. Those with a BW-to-BSA ratio of more than 1 were allocated to the "relatively over-dosed group" (n = 32), while the remaining patients with a ratio of less than 1 were assigned to the "relatively under-dosed" group (n = 28).

Ethical Approval

This study was approved by the Ethical Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2022/42-14, date: 28.12.2022) and performed according to the principles of the Declaration of Helsinki. Informed consent to participate in the study was obtained from all participants (or their parents or legal guardian in the case of children under 16).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences, version 24 for Windows (IBM Inc., Armonk, NY, USA). The homogeneity of the data obtained in the study was tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. Numerical variables were not normally distributed and so non-parametric presentation was used; median [interquartile range (IQR)], unless otherwise stated. The correlation between the actual and estimated doses was assessed with Spearman's correlation test (r_s). Categorical variables were analyzed by chi-square or Fisher's exact test. All tests were two-tailed, and a p value of less than 0.05 was taken as statistically significant.

Results

The study included 60 patients with IGHD, of whom 18 (30%) were girls, and the whole cohort had a median (IQR) age of 11.9 (3.8) years. Table 1 summarizes the characteristics of all patients and the comparison of patients with HAG vs NHAG. Of the 60 patients, 36 (60%) were classified as HAG after one year of treatment. Overall, the median (IQR) dose administered per kg BW (mcg/kg/day) was reduced significantly over 1-year period [30 (4) and 27.6 (7) mcg/kg/day; p = 0.007]. While the doses were similar in the prepubertal group [30 (5) and 28 (7), p = 0.29, respectively], they were significantly reduced in the pubertal group [30 (1.5) and 26 (7), p = 0.002, respectively]. The two groups classified as HAG and NHAG were not significantly different in terms of sex, ages at the start of treatment, puberty status, rhGH doses, target height, predicted adult height, and SD scores for weight, BMI, IGF-1, and IGFBP-3 (Table 1). The follow-up of the SD scores for weight and height, along with IGF-1 and IGFBP-3 levels are presented in Figure 1. The SD scores for IGF-1 levels were in the reference ranges at the end of the first year of treatment. IGF-1 levels were not correlated with the prescribed doses ($r_s = 0.164$, $p = 0.22$; $r_s = 0.14$, $p = 0.3$; $r_s = 0.14$, $p = 0.3$, according to BW and BSA calculated either by Costeff's and Mosteller's formulas, respectively).

The estimated daily doses calculated for BSA using Costeff's and Mosteller's formulas were strongly correlated [(r_s) = 0.974, $p < 0.001$]. The actual daily doses given, based on BW and the estimated doses calculated according to BSA were also strongly correlated (Spearman's correlation (r_s) = 0.990, $p < 0.001$; (r_s) = 0.977, $p < 0.001$, BSA calculated with Costeff's and Mosteller's formulas, respectively). The median BW-to-BSA was 1 (0.2), with a full range of 0.65 to 1.34, while BSA-to-BW ratio ranged from 0.75 to 1.53. The ratio of the dose given based on BW and the dose calculated according to BSA were positively correlated both with the ages and BMI of the patients for both Costeff's formula, (r) = 0.814, $p < 0.001$, (r) = 0.776, $p < 0.001$ and Mosteller's formula (r) = 0.747, $p < 0.001$, (r) = 0.797, $p < 0.001$) (Figure 2). As shown in Figure 2a, b, the ratio of BW-to-BSA was equal to 1 at the age of approximately 11 years with a BMI of 18 kg/m^2. The slopes and the intercepts calculated for the best-fit lines for both Costeff's and Mosteller's formulas yielded similar results (age: Costeff's formula: Y = 0.03331*X + 0.6254; Mosteller's formula: Y = 0.03587*X + 0.6009; BMI: Costeff's formula: Y = 0.03250*X + 0.4222; Mosteller's formula: Y = 0.03939*X + 0.3043).

Table 1. The clinical and laboratory characteristics of the patients

Clinical and laboratory characteristics	All patients, (n = 60)	Height gain at goal, (n = 36)	Height gain not at goal, (n = 24)	p[a]
At GH start				
Age, years	11.9 (3.8)	11.9 (5.3)	12 (2.8)	0.39
Prepubertal (%)	35 (58%)	21/36 (58%)	14/24 (58%)	1.00[b]
Weight, SDS	-1.9 (1.4)	-2.2 (1.8)	-1.7 (1)	0.12
BMI, SDS	-0.5 (1.5)	-0.6 (1.7)	-0.4 (0.9)	0.83
Height, SDS	-2.8 (1)	-3.1 (1.1)	-2.5 (0.6)	**0.02**
Bone age, years	9 (5)	7.8 (6.8)	9.8 (3.4)	0.12
Target height	165.5 (11.8)	166 (12)	166 (9)	0.71
Target height, SDS	-1.2 (1.1)	-1 (1.4)	-1.6 (1.6)	0.13
Predicted adult height	162.6 (13.7)	161 (15)	163 (10)	0.15
Predicted adult height, SDS	-1.5 (1.4)	-1.8 (1.7)	-1.5 (1.2)	0.9
IGF-1 at the start, SDS	-1.2 (1.2)	-1.3 (1.4)	-1.0 (1.3)	0.24
IGFBP-3 at start, SDS	-0.6 (1.6)	-0.7 (1.9)	-0.5 (1.3)	0.73
Peak GH responses, ng/mL	4.3 (4)	4.3 (3.4)	4.1 (4)	0.37
GH doses				
mcg/kg/day	30 (4)	30 (3.5)	30 (4)	0.78
mg/m^2/day (Costeff)	0.8 (0.4)	0.8 (0.4)	0.8 (0.3)	0.84
mg/m^2/day (Mosteller)	0.8 (0.4)	0.8 (0.4)	0.8 (0.3)	1
At 1st year of GH treatment				
Height, SDS	-2.2 (1)	-2 (1.4)	-2.2 (0.8)	0.14
Weight, SDS	-1.7 (1.4)	-1.7 (1.6)	-1.2 (1)	0.82
BMI, SDS	-0.4 (1.3)	-0.5 (1.6)	-0.2 (1)	0.88
Bone age, years	11 (4.6)	10.5 (7.5)	11 (2.5)	0.40
GH dose, mcg/kg/day	27.6 (7)	28 (7.5)	27 (8.2)	0.64
Predicted adult height	167.3 (15.7)	167 (15)	170 (13)	0.5
IGF-1, SDS	0.6 (1.2)	0.5 (1.7)	0.8 (1.3)	0.47
IGFBP-3, SDS	0.4 (1.5)	0.4 (1.7)	0.7 (1)	0.10
Annual Δ Height SDS	0.6 (0.5)	0.9 (0.6)	0.3 (0.3)	**0.02**

Data are given as median (interquartile range). [a]Mann-Whitney U test. [b]Chi-squared test.
GH: growth hormone, SDS: standard deviation scores, BMI: body mass index, IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3, Annual Δ height: height at 1st year of treatment - height at start of treatment

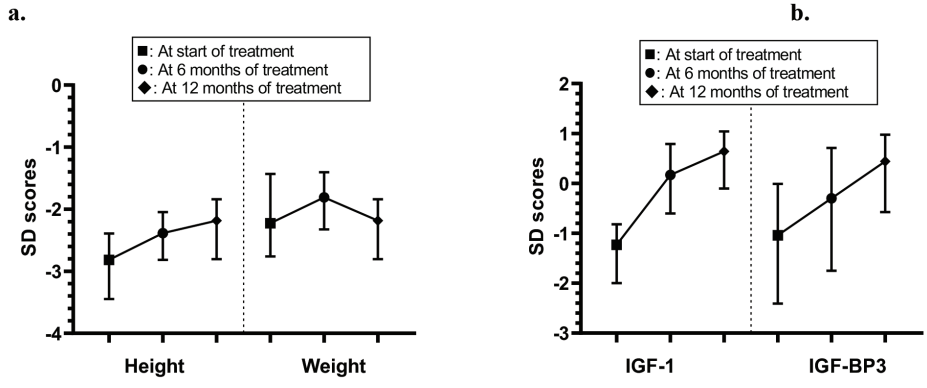

Figure 1. The standard deviation scores for a) auxological measurements for height and weight and b) laboratory tests for IGF-1 and IGFBP-3 levels. The symbols represent median values and the vertical bars indicate the interquartile range

SD: standard deviation, IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3

Table 2 shows the number and percentages of patients according to growth responses (HAG, NHAG) and relative dose estimations (relatively over- and under-dosed groups). The relative dose estimations (relative over- and under-dosed groups) differed significantly between the patients classified as HAG or NHAG. Fifty-six percent of patients in the NHAG group compared to 44% of patients in the HAG group received relatively higher doses, while 79% of patients classified as HAG compared to 21% of patients classified as NHAG received relatively lower doses (p = 0.006). When the patients were subdivided according to their pubertal status, the results showed that higher doses were administered mostly to the pubertal patients in both NHAG and HAG groups (10/18; 56% and 11/14; 79%, respectively). In the pre-pubertal age group, 73% of patients classified as NHAG compared to 27% of patients in the HAG group received relatively higher doses, while 25% of patients classified as NHAG compared to 75% of patients classified as HAG received relatively lower doses (p = 0.01). In the pubertal groups, patients in the NHAG and HAG groups received comparable doses (p = 0.125) (Table 2).

Discussion

In this study, differences between the BW- and BSA-based dosing methods have emerged in children. We have shown that rhGH dosage calculations based on BW compared to BSA may result in the administration of relatively higher or lower doses, depending on the ages and BMIs of the patients, which may be particularly important in patients with good growth responses.

The notion that BW- and BSA-based dosages are equivalent has been examined by various studies in several disciplines, and the potential risks of over and undertreatment have

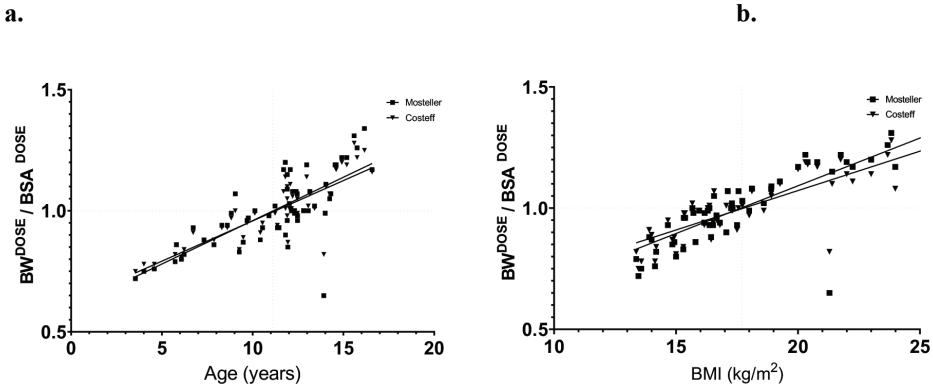

Figure 2. a) The ratio between the actual dose given in body surface area (calculated according to Mosteller's and Costeff's formulas) and the dose calculated per body weight versus age (years) is shown. The equations for the slopes are as following: Costeff's formula: Y = 0.03331*X + 0.6254; Mosteller's formula: Y = 0.03587*X + 0.6009. b) Body surface area/body weight -based dose ratio versus body mass index (kg/m^2). The equations for the slopes are as following: Costeff's formula: Y = 0.03250*X + 0.4222; Mosteller's formula: Y = 0.03939*X + 0.3043. Squares indicate doses calculated based on Mosteller's formula, triangles indicate doses calculated based on Costeff's formula

BW: body weight, BSA: body surface area, BMI: body mass index

Table 2. The comparison of groups that were relatively over- and underdosed

Characteristics	All patients, (n = 60)	Height gain at goal, (n = 36)	Height gain not at goal, (n = 24)	p
Relatively over-dosed group	32/60 (53%)	14/32 (44%)	18/32 (56%)	**0.006**[a]
Relatively under-dosed group	28/60 (47%)	22/28 (79%)	6/28 (21%)	
Prepubertal subgroup, (n = 35)				
Relatively over-dosed group	11/35 (31%)	3/11 (27%)	8/11 (73%)	**0.01**[b]
Relatively under-dosed group	24/35 (69%)	18/24 (75%)	6/24 (25%)	
Pubertal subgroup, (n = 25)				
Relatively over-dosed group	21/25 (84%)	11/21 (52%)	10/21 (48%)	0.125[b]
Relatively under-dosed group	4/25 (16%)	4/4 (100%)	0/4 (0%)	

Number (n) of patients with percentages (%) are presented. Dose ratio was calculated as following: Dose given according to body weight [body weight (BW); mg]/dose calculated according to body surface area (BSA); mg. Over-dosed group indicates a dose ratio of BW-to-BSA greater than 1; under-dosed group indicates a dose ratio of less than or equal to 1. BSA was calculated according to Mosteller's formula.
[a]: Pearson chi-square test, [b]: Fisher's exact test

been established (6,28,29,30,31). Both strategies were assumed to be equally effective in treatment, with significant differences only observed at the extremes of weight and in very young patients (32). In contrast to the general belief of equal efficacy, Hughes et al. (7) demonstrated that even slight increases in BW-based doses could correspond to higher values when converted to mg/m^2/week. The results of the present study indicate that the difference between BW- and BSA-based dosing increased proportionally as patients' age and BMI values increased. The actual and estimated doses were equal at the age of approximately 11 years with a BMI level of 18 kg/m^2. Thus, older patients with higher BMIs would be given higher doses if BW-based methods were chosen over BSA-based calculations.

Due to the variations in the pharmacokinetics of medications resulting from changes in growth and maturity, dosage recommendations for children are often subdivided into age categories of 2-6 years, 6-12 years, 12-18 years, and 18-21 years (33). Likewise, the Pediatric Pharmacy Advocacy Group (33,34) also recommends BW-based dosing for children weighing less than 40 kg. Even though these strategies have not been generalized for patients who are receiving rhGH treatment, different dosing strategies have also been explored among girls with Turner syndrome (8). Similar results were seen in the homogenous group of patients with IGHD with similar characteristics in the present study, also suggesting that different efficacy and safety profiles may result for different age groups.

Differences were also found between the estimations based on BW and BSA when patients were stratified by response to treatment in terms of height gained. Among patients in the HAG or NHAG groups, the percentages of patients who would be have been given relatively higher or lower doses of rhGH differed significantly. Fifty six percent of all patients classified as NHAG, most of whom were pubertal, received higher doses when using BW-based in comparison to BSA-based calculations. Furthermore, almost three-quarters of pre-pubertal patients (73%) classified as NHAG were given relatively higher doses using BW-based calculation. This could suggest that this method based on BW would be preferable in both prepubertal and pubertal groups with inadequate height gain, since BSA-based estimates would result in the administration of relatively lower doses to those with poor growth responses. However, these associations should be interpreted carefully. Although the differences were not significant, patients in the NHAG group had relatively shorter target heights and older bone ages, with statistically significant lower height SD scores at start compared to patients in the HAG group, all of which may be indicative of poor growth response (35). Moreover, it is also impossible to predict whether higher doses would have resulted in better growth responses.

Futhermore, dosing based on BW resulted in lower but adequate doses for those exhibiting the expected growth response (HAG group). In other words, if dosing based on BSA had been chosen, the majority of patients with HAG (79%) would have received unnecessarily high doses of rhGH, whereas patients in the NHAG group (56%) would have been dosed relatively inadequately low. For patients with the expected height gain in the first year (HAG), subgroup analysis showed that the relative dose difference in favor of BW-based calculations was mostly attributable to the prepubertal group. Among the prepubertal HAG patients, 75% would have been dosed relatively higher if the BSA-based method had been chosen. Similarly, Hughes et al. (7) suggested that BSA-based dosing would result in overtreatment for most children, including those with Turner syndrome and GHD, but not excluding those with obesity. Similar to our findings, both Schrier et al. (8) indicated that younger children would receive more rhGH doses based on BSA in comparison to BW-based doses (11).

These results are important because of the two main drawbacks associated with relative overtreatment with rhGH. Firstly, excessive rhGH may result in potential adverse effects. IGF-1 and IGFBP-3 levels were monitored and were in the reference ranges for our cohort who actually received rhGH doses based on BW while if relatively higher doses had been given using BSA-based methods, there may have been a need for more frequent dose adjustments or clinic visits. Secondly, prescribing higher GH doses to good responders would also result in unnecessary expenditure. Schrier et al. (8) also demonstrated that, despite comparable efficacy, the predicted financial savings for rhGH doses based on BSA and BW would be significantly different. Similarly, the ratio of BSA-to-BW extended to 1.53, indicating that if dosing based on BSA rather than BW had been adopted, the costs would have been 53% higher, despite equal efficacy. Considering that GH treatment is expensive, with an average annual cost of up to 7,088 Euros for a 30-kg child with GH deficit, for children younger than 11 years with BMI levels less than 18, the BSA-based dosage would not be cost-effective in comparison to the BW-based calculations (36).

Study Limitations

Our study was retrospective and we were not able to prescribe both dosings randomly to a larger cohort due to ethical and logistical barriers. Furthermore, due to small group size, we were not able to draw robust conclusions concerning the pubertal group. Another weakness was that the study included two different centers but both

centers have been following identical strategies regarding follow-up and rhGH dosing. The greatest strength of our study was that none of the patients had been taking any additional medications, and the safety of treatment was strictly controlled by routinely measured IGF-1/IGFBP-3 values. Thus, the two dosing strategies were hypothetically compared in a homogenous cohort with IGHD who were not overweight and did not have any co-morbidities.

Conclusion

BW- and BSA-based strategies were compared in an homogenous cohort of patients with IGHD receiving rhGH. GH doses based on BW compared to BSA-based dosing may result in the administration of higher doses to children older than 11 years of age with BMI greater than 18 kg/m^2 and lower doses to children younger than 11 years of age with BMI less than 18 kg/m^2. Dosing based on BW may be preferable in both prepubertal and pubertal children who do not show adequate growth responses. In prepubertal children, relatively lower doses calculated based on BW rather than BSA provide similar efficacy at lower costs.

Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2022/42-14, date: 28.12.2022) and performed according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Ayhan Abacı conceived the idea for this work. Özge Besci and Ayhan Abaci designed the study. Özge Besci, Sezen Ersoy, Reyhan Deveci Sevim, Kübra Yüksek Acinikli, Gözde Akın Kağızmanlı, Ahmet Anık, and Tolga Ünüvar have collected and interpreted the data. Özge Besci wrote the first draft. Korcan Demir, Ece Böber and Ayhan Abacı edited and revised the manuscript critically. All authors read and approved the final manuscript.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ranke MB, Wit JM. Growth hormone - past, present and future. Nat Rev Endocrinol. 2018;14:285-300. Epub 2018 Mar 16
2. Hage C, Gan HW, Ibba A, Patti G, Dattani M, Loche S, Maghnie M, Salvatori R. Advances in differential diagnosis and management of growth hormone deficiency in children. Nat Rev Endocrinol 2021;17:608-624. Epub 2021 Aug 20
3. Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. N Engl J Med 2019;380:2551-2562.
4. Collett-Solberg PF, Ambler G, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, Cheung PT, Choong CSY, Cohen LE, Cohen P, Dauber A, Deal CL, Gong C, Hasegawa Y, Hoffman AR, Hofman PL, Horikawa R, Jorge AAL, Juul A, Kamenický P, Khadilkar V, Kopchick JJ, Kriström B, Lopes MLA, Luo X, Miller BS, Misra M, Netchine I, Radovick S, Ranke MB, Rogol AD, Rosenfeld RG, Saenger P, Wit JM, Woelfle J. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr 2019;92:1-14. Epub 2019 Sep 12
5. Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, Murad MH; Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr 2016;86:361-397. Epub 2016 Nov 25
6. Feber J, Al-Matrafi J, Farhadi E, Vaillancourt R, Wolfish N. Prednisone dosing per body weight or body surface area in children with nephrotic syndrome: is it equivalent? Pediatr Nephrol 2009;24:1027-1031.
7. Hughes IP, Harris M, Cotterill A, Ambler G, Cowell CT, Cutfield WS, Werther G, Choong CS. Comparison of weight- vs body surface area-based growth hormone dosing for children: implications for response. Clin Endocrinol (Oxf) 2014;80:384-394.
8. Schrier L, de Kam ML, McKinnon R, Che Bakri A, Oostdijk W, Sas TC, Menke LA, Otten BJ, de Muinck Keizer-Schrama SM, Kristrom B, Ankarberg-Lindgren C, Burggraaf J, Albertsson-Wikland K, Wit JM. Comparison of body surface area versus weight-based growth hormone dosing for girls with Turner syndrome. Horm Res Paediatr 2014;81:319-330. Epub 2014 Apr 23
9. Poyrazoğlu Ş, Akçay T, Arslanoğlu İ, Atabek ME, Atay Z, Berberoğlu M, Bereket A, Bideci A, Bircan İ, Böber E, Can Ş, Cesur Y, Darcan Ş, Demir K, Dündar B, Ersoy B, Esen İ, Güven A, Kara C, Keskin M, Kurtoğlu S, Memioğlu N, Özbek MN, Özgen T, Sarı E, Şıklar Z, Şimşek E, Turan S, Yeşilkaya E, Yüksel B, Darendeliler F. Current practice in diagnosis and treatment of growth hormone deficiency in childhood: a survey from Turkey. J Clin Res Pediatr Endocrinol 2015;7:37-44.
10. Juul A, Bernasconi S, Clayton PE, Kiess W, DeMuinck-Keizer Schrama S; Drugs and Therapeutics Committee of the European Society for Paediatric Endocrinology (ESPE). European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency. Horm Res 2002;58:233-241.
11. Betts PR, Butler GE, Donaldson MD, Dunger DB, Johnston DI, Kelnar CJ, Kirk J, Price DA, Wilton P. A decade of growth hormone treatment in girls with Turner syndrome in the UK. UK KIGS Executive Group. Arch Dis Child 1999;80:221-225.
12. Hawcutt DB, Bellis J, Price V, Povall A, Newland P, Richardson P, Peak M, Blair J. Growth hormone prescribing and initial BMI SDS: Increased biochemical adverse effects and costs in obese children without additional gain in height. PLoS One 2017;12:e0181567.
13. Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. Pharmacotherapy 2012;32:856-868. Epub 2012 Jun 18
14. Langbakke IH, Nielsen JN, Skettrup MP, Harper A, Klitgaard T, Weil A, Engelhardt E, Lange M. Pharmacokinetics and pharmacodynamics of growth hormone in patients on chronic haemodialysis compared with matched healthy subjects: an open, nonrandomized, parallel-group trial. Clin Endocrinol (Oxf) 2007;67:776-783. Epub 2007 Jul 18

15. Zanforlini BM, Alessi A, Pontarin A, De Rui M, Zoccarato F, Seccia DM, Trevisan C, Brunello A, Basso U, Manzato E, Sergi G. Association of body surface area with fat mass, free fat mass and total weight in healthy individuals, and implications for the dosage of cytotoxic drugs. Clin Nutr ESPEN 2021;43:471-477. Epub 2021 Mar 16
16. Redlarski G, Palkowski A, Krawczuk M. Body surface area formulae: an alarming ambiguity. Sci Rep 2016;6:27966.
17. Vestergaard B, Thygesen P, Kreilgaard M, Fels JJ, Lykkesfeldt J, Agersø H. The kidneys play a central role in the clearance of rhGH in rats. Eur J Pharm Sci 2016;86:29-33. Epub 2016 Mar 2
18. Collipp PJ, Patrick JR, Goodheart C, Kaplan SA. Distribution of tritium labeled human growth hormone in rats and guinea pigs. Proc Soc Exp Biol Med 1966;121:173-177.
19. Sıklar Z, Öcal G, Berberoğlu M, Bilir P. Combined evaluation of IGF-1 and IGFBP-3 as an index of efficacy and safety in growth hormone treated patients. J Clin Res Pediatr Endocrinol 2009;1:240-243. Epub 2009 Aug 5
20. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Front Endocrinol (Lausanne) 2021;12:720419.
21. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170-179.
22. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist: Stanford University Press, 1959.
23. Roche AF, Wainer H, Thissen D. The RWT method for the prediction of adult stature. Pediatrics 1975;56:1027-1033.
24. Demir K, Konakçı E, Özkaya G, Kasap Demir B, Özen S, Aydın M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations. J Clin Res Pediatr Endocrinol 2020;12:125-129. Epub 2019 Sep 2
25. Costeff H. A simple empirical formula for calculating approximate surface area in children. Arch Dis Child 1966;41:681-683.
26. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
27. Pozzobon G, Partenope C, Mora S, Garbetta G, Weber G, Barera G. Growth hormone therapy in children: predictive factors and short-term and long-term response criteria. Endocrine 2019;66:614-621. Epub 2019 Aug 18
28. Saadeh SA, Baracco R, Jain A, Kapur G, Mattoo TK, Valentini RP. Weight or body surface area dosing of steroids in nephrotic syndrome: is there an outcome difference? Pediatr Nephrol 2011;26:2167-2171. Epub 2011 Jul 16
29. Raman V, Krishnamurthy S, Harichandrakumar KT. Body weight-based prednisolone versus body surface area-based prednisolone regimen for induction of remission in children with nephrotic syndrome: a randomized, open-label, equivalence clinical trial. Pediatr Nephrol 2016;31:595-604. Epub 2016 Jan 12
30. Camaione L, Elliott K, Mitchell-Van Steele A, Lomaestro B, Pai MP. Vancomycin dosing in children and young adults: back to the drawing board. Pharmacotherapy 2013;33:1278-1287. Epub 2013 Sep 9
31. Li X, Zhang Y, Liu H, Jiang H, Ge H, Zhang Y. Pediatric Dosing of Intravenous Sotalol Based on Body Surface Area in Patients with Arrhythmia. Pediatr Cardiol 2017;38:1450-1455. Epub 2017 Jul 28
32. Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr 2013;79:51-67. Epub 2013 Feb 26
33. Gerhart JG, Balevic S, Sinha J, Perrin EM, Wang J, Edginton AN, Gonzalez D. Characterizing Pharmacokinetics in Children With Obesity-Physiological, Drug, Patient, and Methodological Considerations. Front Pharmacol 2022;13:818726.
34. Matson KL, Horton ER, Capino AC; Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Medication Dosage in Overweight and Obese Children. J Pediatr Pharmacol Ther 2017;22:81-83.
35. de Ridder MA, Stijnen T, Hokken-Koelega AC. Prediction of adult height in growth-hormone-treated children with growth hormone deficiency. J Clin Endocrinol Metab 2007;92:925-931. Epub 2006 Dec 19
36. Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, Milne R. Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. Health Technol Assess 2002;6:1-168.