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

Running title: Body weight versus body surface area

Özge Besci1, Reyhan Deveci Sevim2, Kübra Yüksek Acinikli1, Gözde Akın Kağızmanlı1, Sezen Ersoy1, Korcan Demir1, Tolga Ünivar3, Ece Böber1, Ahmet Anik2, Ayhan Abacı1
1Division of Pediatric Endocrinology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
2Division of Pediatric Endocrinology, Aydın Adnan Menderes University Faculty of Medicine, Aydın, Turkey
3Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

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 11.7 years of age with BMI levels less than 18.3 kg/m2, growth hormone dosing based on body weight may be preferable.

ABSTRACT

Introduction: Body weight (BW) and body surface area (BSA)-based dosing regimens have been recommended for recombinant human growth hormone (rhGH) replacement, with the assumption that they are equally efficacious. We wanted to determine if higher or lower treatment may result from either of the two regimens based on the initial prescribed doses and the growth responses of the patients throughout the first year of therapy.

Methods: The retrospective study included 60 children from two different centers, aged 1-18 years, with the diagnosis of idiopathic isolated growth hormone deficiency (IGHD). BW-based dosing in mcg/kg/day, which is routinely employed in our clinical practice, was converted to BSA in mg/m2/day to determine the equivalent amounts of the given rhGH. Those with a BSA-to-BW ratio of more than 1 were allocated to the "relatively higher-dosed group", while the remaining patients were assigned to the "relatively lower-dosed" group. Patients with a height gain greater than 0.5 standard deviation (SD) score at the end of one year were classified as the height at goal (HAG), whereas those with a height gain of less than 0.5 SD score were assigned as the height not at goal (NHAG).

Results: The study included 60 patients (18 girls, 42 boys) with IGHD. Thirty-six (60%) patients had HAG after one year of treatment. The ratio of dosing based on BSA to BW was negatively correlated both with the ages and BMI levels of the patients, leveling off at the age of 11.7 at a BMI of 18.3 kg/m2. The relative dose estimations (relatively higher-dosed groups) differed significantly between the patients with HAG and NHAG (p=0.006). If dosing had been based on BSA rather than BW, the majority of patients with HAG (61%) would have been dosed relatively higher, whereas those with NHAG (75%) would have been dosed relatively lower.

Conclusion: We have evaluated BSA and BW-based strategies among a homogenous cohort of patients with IGHD. GH doses based on BSA compared to BW-based dosing may result in the administration of higher doses to children younger than 11.7 years of age with BMI levels less than 18.3 kg/m2 and lower doses to children older than 11.7 years of age with BMI levels more than 18.3 kg/m2. Dosing based on BW rather than BSA may be preferable in children younger than 11 years old who are not obese.

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

Prof. Dr. Ayhan ABACI, Dokuz Eylül University, Faculty of Medicine, 35340, Inciralti-Balcova, Izmir, Turkey. ayhanabaci@gmail.com +905054776604 0000-0002-1812-0321 28.12.2022 27.03.2023

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Introduction

Growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis dysfunction can 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 profiles, and decreased cardiac function(1-3). The diagnosis of GH deficiency (GHD) is crucial and is accomplished by combining medical history, auxologic measures, biochemical markers, and radiologic 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 advised for rhGH replacement, presuming they are equally effective(5,6). Yet, some countries still choose one regimen over the other(7-11).

Nevertheless, under certain circumstances, the differences between the two dosing regimens may be readily 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 overexposure 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 concentrated predominantly 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 concerning BSA or BW. Homogenous studies on BW and BSA-based dosing strategies are needed. In this paper, we designed a study 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, we wanted to assess whether any of the two regimens would result in higher or lower treatment.

Patients and Methods

Patients

The retrospective study included 60 children aged 1–18 years from two different centers. Individuals with obesity (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. The children with short stature who had IGHD and were treated with rhGH for at least one year between 2017 and 2022 were included. GH deficiency 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 (i.e., clonidine, insulin tolerance test, and levodopa)(2,9). Isolated deficiency indicates the existence 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 the efficacy and IGF-1/IGFBP-3 levels were monitored in order to avoid excessive dosing to ensure safety of the treatment(2,4,19,20). The clinical and laboratory data were monitored every 6–12 months to adjust the 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(21)]; bone age [calculated according to Greulich and Pyle Atlas(22)]; 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/m2), target height (mother’s height + father’s height)(2±6.5, (cm)), predicted adult height [calculated according to the Roche-Wainer-Thissen method(23), (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 reevaluated 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/m2/day. Assuming that the average BW of a child with a BSA of 1 m2 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/m2/day, respectively.

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

i. Costeff’s Formula(25): BSA (m2) = \frac{\text{weight (kg)} + 90}{3600} \times \text{height (cm)}

ii. Mosteller’s Formula(26): BSA (m2) = \sqrt{\frac{\text{weight (kg)} + 90}{3600} \times \text{height (cm)}}

Finally, initially prescribed doses based on BW (mcg/kg/day) and the hypothetically calculated doses based on BSA (mg/m2/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 GH 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 assigned 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 under-dosed group” (n=32). The remaining patients were assigned to the “relatively over-dosed group” (n=28).

Statistical analysis

Statistical analyses were performed using SPSS v.24 for Windows. The homogeneity of the data obtained in the study was tested using Shapiro-Wilk and Kolmogorov-Smirnov Tests. The numeric variables did not comply with normal distribution; thus, the data are expressed as medians and interquartile range (IQR) unless otherwise stated. The relationship between the actual and estimated doses were correlated based on Spearman’s correlation test (r). 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.

Ethical approval

This study was approved by the ethical committee of İzmir Dokuz Eylül University Faculty of Medicine (Ethics approval number: 2022/42-14) 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).

Results

The study included 60 patients [18 (30%) girls; median (IQR) age of 11.9 (3.8) years] with IGHD. Table 1 summarizes the characteristics of all patients and the comparison of patients with HAG vs NHAG. Of the 60 patients, 36 (60%) had 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 of 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 3). 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 first year of treatment. The IGF-1 levels were not correlated with the prescribed doses (r=0.164, p=0.22; r=-0.14, p=0.3; r=-0.14, p=0.3, according to BW and BSA (BSA calculated per Costeff’s and Mosteller’s formulas, respectively)).

The estimated daily doses calculated per Costeff’s and Mosteller’s formulas were strongly correlated (r= 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) = 0.990, p=0.001; (r) =0.977, p<0.001). The median BW-to-BSA ratio was 1 (0.2), with a range of minimum 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 levels of the patients (Costeff’s formula, (r) = 0.814, p<0.001, (r) = 0.776 (p<0.001); Mosteller’s formula, (r) = 0.747, p<0.001, (r) = 0.797, p<0.001) (Figure 2). As shown in Figure 2a and 2b, the
ratio of BW-to-BSA was equal to 1 approximately at the age of 11 at a BMI level of 18 kg/m². 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; BSA: Costeff’s formula: Y = 0.03509*X + 0.4222; Mosteller’s formula: Y = 0.03939*X + 0.3043). 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 with HAG and NHAG. Fifty-six percent of patients with NHAG compared to 44% of patients with HAG received relatively higher doses, while 70% of patients with HAG compared to 21% of patients with 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 administrated 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 with NHAG compared to 27% of patients with HAG received relatively higher doses, while 75% of patients with NHAG compared to 75% of patients with HAG received relatively lower doses (p=0.01). In the pubertal groups, patients with NHAG and HAG (48% vs 52%, and 0% vs 27%, respectively) received comparable doses (p=0.125). (Table 2).

Discussion

In this study, we have established differences between the BW- and BSA-based dosing methods. We have demonstrated that rhGH dosage calculations based on BW compared to BSA may result in the administration of relatively higher or lower doses according to the ages and BMI levels of the patients, which may be particularly noteworthy for patients with good growth responses. Furthermore, dosing based on BW resulted in adequately low doses for those on HAG. In other terms, if dosing based on BSA had been chosen, the majority of patients with HAG (79%) would have been dosed relatively unnecessarily higher, whereas those with NHAG (56%) would have been dosed relatively inadequately lower. For patients with HAG, the subgroup analysis showed that the relative dose difference in favor of BW-based calculations was mostly attributable to the prepubertal group. Among the prepubertal patients with HAG, 75% would have been dosed relatively higher if BSA method had been chosen. These findings demonstrated that BSA-based rhGH administration would result in higher doses to prepubertal children despite equal efficacy. Similarly, Hughes et al.(7) demonstrated that even slight dose increments in BW-based doses could correspond to higher values in mg/kg/week. Based on our findings, the difference between BW and BSA increased proportionally as patients’ age and BMI values increased. Our results demonstrated that the actual and estimated doses were equal at the age of 11 with a BMI level of 18 kg/m². The older patients with higher BMI levels would be given higher dosages if BW-based methods were chosen over BSA-based calculations. Dosages in the pharmacokinetics of medications vary from changes in growth and puberty, 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 our homogenous group of patients with IGHD with similar characteristics. Our findings also indicated that different profiles of efficacy and safety may result for different age groups.

Based on the height responses of the patients, we have demonstrated differences between the estimations based on BW and BSA. Among patients with HAG and NHAG, the percentages of patients who would be administrated relatively higher or lower doses of rhGH differed significantly. Fifty-six percent of all patients with NHAG, most of whom constituted the pubertal patients, received higher doses in BW in comparison to BSA based calculations. In fact, a greater percentage of pre-pubertal patients (73%) with NHAG were given relatively higher doses. This could suggest that BW-based calculations would be a more preferable option in both prepubertal and pubertal groups with inadequate height gain, since BSA-estimates would result in the administration of far less dosages to those with poor growth responses. However, these associations should be interpreted carefully. Albeit not reaching statistical significance, those belonging to HAG compared to those with HAG, had relatively shorter target heights and older bone ages, with statistically significant lower height SD scores at start, all of which may be indicative of poor growth response(35). Further, it is also impossible to predict whether higher doses would result in better growth responses.

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 our homogenous group of patients with IGHD with similar characteristics. Our findings also indicated that different profiles of efficacy and safety may result for different age groups.

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OB performed research, analyzed results, and wrote the first draft; KD, EB and AA critically edited the paper. All authors read and approved the final manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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References
Figure 1. The standard deviation (SD) scores for a. auxological measurements for height and weight and b. laboratory tests for IGF-1 and IGF-BP3 levels. The symbols represent median values and the vertical bars indicate the interquartile range.
Figure 2. a. The ratio between the actual dose given in body surface area (BSA; calculated according to Mosteller’s and Costeff’s formulas) and the dose calculated per body weight (BW) versus age (years) is shown. The equations for the slopes are as following: Costeff’s formula: \( Y = 0.03331 \times X + 0.6254 \); Mosteller’s formula: \( Y = 0.03587 \times X + 0.6009 \). b. BSA/BW-based dose ratio versus BMI (kg/m\(^2\)). The equations for the slopes are as following: Costeff’s formula: \( Y = 0.03250 \times X + 0.4222 \); Mosteller’s formula: \( Y = 0.03939 \times X + 0.3043 \). Squares indicate doses calculated based on Mosteller’s formula, triangles indicate doses calculated based on Costeff’s formula.
Table 1. The clinical and laboratory characteristics of the patients.

<table>
<thead>
<tr>
<th>Clinical and Laboratory Characteristics</th>
<th>All patients (n=60)</th>
<th>Height gain at goal (HAG) (n=36)</th>
<th>Height gain not at goal (NHAG) (n=24)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At GH start</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>11.9 (3.8)</td>
<td>11.9 (5.3)</td>
<td>12 (2.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Prepubertal (%)</td>
<td>35 (58%)</td>
<td>21/36 (58%)</td>
<td>14/24 (58%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight, SDS</td>
<td>-1.9 (1.4)</td>
<td>-2.2 (1.8)</td>
<td>-1.7 (1)</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI, SDS</td>
<td>-0.5 (1.5)</td>
<td>-0.6 (1.7)</td>
<td>-0.4 (0.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Height, SDS</td>
<td>-2.8 (1)</td>
<td>-3.1 (1.1)</td>
<td>-2.5 (0.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bone age, years</td>
<td>9 (5)</td>
<td>7.8 (6.8)</td>
<td>9.8 (3.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Target height</td>
<td>165.5 (11.8)</td>
<td>166 (12)</td>
<td>166 (9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Predicted adult height</td>
<td>162.6 (13.7)</td>
<td>161 (15)</td>
<td>163 (10)</td>
<td>0.15</td>
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<td>IGF-1 at the start, SDS</td>
<td>-1.5 (1.4)</td>
<td>-1.8 (1.7)</td>
<td>-1.5 (1.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>IGFBP-3 at start, SDS</td>
<td>-0.6 (1.6)</td>
<td>-0.7 (1.9)</td>
<td>-0.5 (1.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Peak GH responses, ng/mL</td>
<td>4.3 (4)</td>
<td>4.3 (3.4)</td>
<td>4.1 (4)</td>
<td>0.37</td>
</tr>
<tr>
<td>GH doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mcg/kg/day</td>
<td>30 (4)</td>
<td>30 (3.5)</td>
<td>30 (4)</td>
<td>0.78</td>
</tr>
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<td>mg/m²/day (Costeff)</td>
<td>0.8 (0.4)</td>
<td>0.8 (0.4)</td>
<td>0% (0.5)</td>
<td>0.84</td>
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<tr>
<td>mg/m²/day (Mosteller)</td>
<td>0.8 (0.4)</td>
<td>0.8 (0.4)</td>
<td>0% (0.3)</td>
<td>0.7</td>
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<tr>
<td><strong>At 1st year of GH treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Height, SDS</td>
<td>-2.2 (1)</td>
<td>-2 (1.4)</td>
<td>-2.2 (0.8)</td>
<td>0.14</td>
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<td>Weight, SDS</td>
<td>-1.7 (1.4)</td>
<td>-1.7 (1.6)</td>
<td>-1.2 (1)</td>
<td>0.82</td>
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<td>BMI, SDS</td>
<td>-0.4 (1.3)</td>
<td>-0.5 (1.6)</td>
<td>-0.2 (1)</td>
<td>0.88</td>
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<tr>
<td>Bone age, years</td>
<td>11 (4.6)</td>
<td>10.5 (7.5)</td>
<td>11 (2.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>GH dose, mcg/kg/day</td>
<td>27.6 (7)</td>
<td>28 (7.5)</td>
<td>27 (8.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Predicted adult height</td>
<td>167.3 (15.7)</td>
<td>167 (15)</td>
<td>170 (13)</td>
<td>0.5</td>
</tr>
<tr>
<td>IGF-1, SDS</td>
<td>0.6 (1.2)</td>
<td>0.5 (1.7)</td>
<td>0.8 (1.3)</td>
<td>0.47</td>
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<tr>
<td>IGFBP-3, SDS</td>
<td>0.4 (1.5)</td>
<td>0.4 (1.7)</td>
<td>0.7 (1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Annual Δ Height SDS</td>
<td>0.6 (0.5)</td>
<td>0.9 (0.6)</td>
<td>0.3 (0.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are given as median (interquartile range).

*aMann-Whitney U test.  
bChi-squared test.

Abbreviations: SDS: standard deviation scores; BMI: body mass index; GH: growth hormone; IGF: insulin-like growth factor; IGFBP-3: Insulin-like Growth Factor Binding Protein 3; Annual Δ height: height at 1st year of treatment – height at start of treatment.

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

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

Number (n) of patients with percentages (%) are presented. Dose ratio was calculated as following: Dose given according to 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.

*Pearson Chi-square test and bFisher’s exact test.