Comparison of Body Surface Area versus Weight-Based Growth Hormone Dosing for Girls with Turner Syndrome

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\textbf{Key Words}
Turner syndrome \cdot Growth hormone therapy \cdot Body surface area \cdot Body weight \cdot Cost-effectiveness \cdot Adult height

\textbf{Abstract}
\textbf{Background/Aims:} Growth Hormone (GH) dosage in childhood is adjusted for body size, but there is no consensus whether body weight (BW) or body surface area (BSA) should be used. We aimed at comparing the biological effect and cost-effectiveness of GH treatment dosed per m\textsuperscript{2} BSA in comparison with dosing per kg BW in girls with Turner syndrome (TS). \textbf{Methods:} Serum IGF-I, GH dose, and adult height gain (AHG) from girls participating in two Dutch and five Swedish studies on the efficacy of GH were analyzed, and the cumulative GH dose and costs were calculated for both dose adjustment methods. Additional medication included estrogens (if no spontaneous puberty occurred) and oxandrolone in some studies. \textbf{Results:} At each GH dose, the serum IGF-I standard deviation score remained stable over time after an initial increase after the start of treatment. On a high dose (at 1 m\textsuperscript{2} equivalent to 0.056–0.067 mg/kg/day), AHG was at least equal on GH dosed per m\textsuperscript{2} BSA compared with dosing per kg BW. The cumulative dose and cost were significantly lower if the GH dose was adjusted for m\textsuperscript{2} BSA. \textbf{Conclusion:} Dosing GH per m\textsuperscript{2} BSA is at least as efficacious as dosing per kg BW, and is more cost-effective. © 2014 S. Karger AG, Basel

\textbf{Introduction}
Although recombinant growth hormone (GH) treatment has been registered for several causes of short stature for a long time, there are still unresolved issues regarding the GH dose regimen. One of these is that there are two different methods of adjusting the GH dose to body size, i.e. dosing per kg body weight (BW) or per m\textsuperscript{2} body surface area (BSA), with no consensus as to which is more physiological and effective [1]. This makes it dif-
ficult to compare results of growth studies using these two dosing regimens. In previous reports, a conversion factor of 1 m² = 28 kg has been used; however, the BSA/BW ratio is higher in infants and young children, and in adolescents, particularly if obese, the ratio is considerably lower [1, 2]. Thus, BW-based dosing leads to a relatively low dose in young children and a relatively high dose in adolescents in comparison with BSA-based dosing. So far, only one study has been performed to compare the efficacy of the two dosing modalities [3]. These investigators also proposed an alternative conversion formula.

Although in most countries GH dosing is based on BW, it can be argued that dosing by BSA is theoretically more physiological and cost-effective. The first argument is that in adults, most of the free GH distribution after an injection is limited to the extracellular volume [4–6]. This distribution pattern probably also applies to children, although differences may exist in the distribution volume of certain medications due to differences in body composition [7], protein-binding capacity [8], relative volume of the central nervous system [7], and the permeability of the blood-brain barrier [9]. In children, the extracellular fluid volume correlates better with BSA than with BW [10]. Secondly, in children GH is mainly cleared via the liver [6, 11], while hepatic drug clearance correlates best with BSA [12–14]. Admittedly, this argument may be less important than the first, since GH’s metabolic clearance rate is low and steady state GH levels are not reached during the current once-daily subcutaneous dosing regimens [6, 15]. A third argument in favor of BSA-based dosing in children is that it limits costs compared with dosing based on BW because BW increases faster than BSA with age (a factor of 1.7 for BSA compared with dosing based on BW) because BW in-...
Swedish Studies
Serum IGF-I concentrations were measured at baseline, every 3 months during the first year, and annually thereafter, and determined in duplicate by RIA (Mediagnost GmbH, Tubingen, Germany) [24, 25]. IGF-I was converted to SDS corrected for age, gender, and stage of puberty for these assays [23].

### Analyses and Statistical Methods

**IGF-I SDS over Time**
IGF-I SDS was analyzed for DTO, DTDR, and S1–4, regardless of Ox cotreatment. Girls were grouped into three age categories at the start of GH treatment: <8.00, 8.00–11.99, and ≥ 12 years. Aver-

**GH Dose by Age**
Assuming equal efficacy of a fixed dose per BW or BSA, we cal-

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**Table 1.** Study characteristics of the Dutch and Swedish GH studies in girls with TS

<table>
<thead>
<tr>
<th>Study</th>
<th>Age at GH start, mean ± SD age (years)</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>DTO [17] included: 2–15.99 overall: 8.6±3.9</td>
<td>GH 1.33 mg/m^2/day and placebo or Ox from 8 years; 17β-estradiol or ethinyl estradiol was given from 12 years (5 or 0.05 μg/kg/day, respectively) and doubled after 2 years group A: placebo (n = 46) group B: Ox 0.03 mg/kg/day (n = 44) group C: Ox 0.06 mg/kg/day (n = 39)</td>
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<tr>
<td>DTDR [18] included: 2–10.99 overall: 6.5±2.3</td>
<td>in all groups, 17β-estradiol was given after at least 4 years of GH treatment at age of 12 (5 μg/kg/day in first 2 year; 7.5 μg/kg/day in 3rd year; 10 μg/kg/day thereafter) group A: 1.33 mg/m^2/day throughout (n = 20) group B: 1.33 for 1 year, then 2.0 mg/m^2/day (n = 21) group C: 1.33 for 1 year, 2.0 for 1 year, then 2.67 mg/m^2/day (n = 21)</td>
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<tr>
<td>S1 [19] included: 9–15.99 overall: 12.5±1.8a group 1: 12.3±1.7</td>
<td>group 1: Ox 0.05 mg/kg/day; after 1 year addition of GH 0.033 mg/kg/day without (group 1a, n = 6) or with (group 1b, n = 7) ethinyl estradiol 0.1 μg/kg/day group 2: Ox 0.05 mg/kg/day and GH 0.033 mg/kg/day (n = 17) group 3: Ox 0.05 mg/kg/day and GH 0.033 mg/kg/day and ethinyl estradiol 0.1 μg/kg/day (n = 15); puberty induction by yearly increments of ethinyl estradiol (0.1–0.4 μg/kg/day)</td>
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<tr>
<td>S2 [20] included: 9–15.99 11.3±1.8a</td>
<td>GH 0.033 mg/kg/day and ethinyl estradiol 0.1 μg/kg/day with addition of Ox 0.05 mg/kg/day after 3 years (n = 20) puberty induction by yearly increments of ethinyl estradiol (0.1–0.4 μg/kg/day)</td>
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<tr>
<td>S3 included: 3–8.99 6.2±2.5a</td>
<td>GH 0.033 mg/kg/day from start and Ox 0.05 mg/kg/day from age 11 years (only patients with spontaneous puberty, n = 3)</td>
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<tr>
<td>S4 included: 9–14.99 11.9±2.0a</td>
<td>GH 0.033 mg/kg/day from start and Ox 0.05 mg/kg/day from age 11 years (only patients with spontaneous puberty, n = 11)</td>
<td></td>
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<tr>
<td>S5 included: 3–8.99 7.6±3.0a</td>
<td>GH 0.067 mg/kg/day from start and Ox 0.05 mg/kg/day from age 11 years (n = 13)</td>
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</table>

*Mean age ± SD in all five Swedish studies: 11.2 ± 2.8 (n = 92).
with a BSA of 1 m² (28 kg). Therefore, the calculated daily dose based on BW in DTO was approximately 1.33/28 = 0.0475 mg/kg/day at a BSA of 1 m². In DTDR it was 0.0475 mg/kg/day (group A: 1.33 mg/m²/day, 0.0475–0.071 mg/kg/day (group B: 1.33 mg/m²/day, followed by 2 mg/m²/day after 1 year), and 0.0475 to 0.071 to 0.095 mg/kg/day (group C: 1.33 to 2.0 to 2.67 mg/m²/day in the 1st, 2nd, and 3rd and following years). For the low- and high-dose groups in the Swedish studies, the calculated daily dose by BSA was 0.924 mg/m²/day and 1.848 mg/m², respectively. The mean daily doses per BW or BSA were plotted against patient age and the BW-based dose was expressed as a percentage of the BSA-based dose for each data set.

The effect of BMI SDS (using the 1997 Dutch population reference) [27] was investigated by dividing the girls in DTO into three groups: underweight (BMI SDS <–1.3, normal weight (BMI SDS between –1.3 and +1.3), and overweight (BMI SDS >+1.3).

Adult Height Gain

In all studies, height was measured in cm by at least two trained observers at every visit by a Harpenden stadiometer [17–20] and expressed as SDS for the joint Dutch-Swedish-Danish reference data for TS [28]. AHG for TS was obtained by subtracting modified adult height from adult height [29]. For calculating adult height SDS, the reference value at 18 years was used for all girls irrespective of age at reaching adult height. AHG was calculated for three age groups: <8, 8–11.99, and ≥12 years at start.

The effect of the dosage used in S1–4 (0.033 mg/kg/day) could not be compared with a similar BSA-based dose regimen, and the dosage in the Dutch studies (1.33 mg/m²/day, approx. 1.5 times higher) could not be compared with a BW-based regimen. However, AHG could be compared between S5 (0.067 mg/kg/day) and group B of DTDR (1.33–2.0 mg/m²/day, 4 with spontaneous puberty), for which an unpaired t test was used. For this purpose, all girls in the Swedish group were included, irrespective of Ox co-treatment (5 on GH monotherapy, 8 on GH + Ox).

Cumulative GH Dose and Costs

Within each dataset the average cumulative GH doses by BSA and by BW per age group were calculated (by multiplying or dividing actual doses by 28) and compared with a paired t test. For calculating the hypothetical cumulative dose in DTO, not only the calculated dose of 0.0475 mg/kg/day was investigated, but also the recommended GH doses of 0.045 and 0.050 mg/kg/day [30, 31].

The cumulative amount of GH prescribed was multiplied by EUR 44.32/mg (Genotropin®, www.fk.cvz.nl, 2010, the Netherlands) to obtain cumulative costs.

Results

IGF-I Levels

The mean IGF-I SDS remained stable after an initial increase (fig. 1a–c). In DTO, the mean IGF-I SDS was approximately +1 SDS showing no significant change from 6 months onward, but Ox had a small but statistically significant effect on intercepts (0.71, 1.32, and 1.14 for placebo, Ox 0.03 mg/kg, and Ox 0.06 mg/kg, respectively; fig. 1a). There were no differences between subgroups ac-according to age at the start of GH treatment, and the regression coefficients for the slopes were not statistically different from 0 (p > 0.05). In DTDR, the IGF-I profile was similar for the three dose groups (fig. 1b), but at a higher level (+2 to +3 SDS), and there was a small but statistically significant negative regression coefficient in the three dose groups: mean ± SE –0.10 ± 0.02, –0.05 ± 0.02, and –0.08 ± 0.02 (p < 0.0001, p = 0.0085, and p < 0.0001, respectively).

In S1–4 (fig. 1c), the mean IGF-I SDS was between +1 and 1.5, and showed a slight negative trend: –0.03 ± 0.10 and –0.10 ± 0.06 for GH alone or with Ox (p = 0.77 and 0.08, respectively). No data were available for S5.

Effects of Dose Regimen on GH Dose by Age

Figure 2a shows the actual dose administered in DTO compared with a calculated dose based on BW dosing. BW-based dosing would lead to a lower dose than BSA-based dosing in girls below 10 years of age, and a higher dose above 10 years. A similar pattern was observed in group B of DTDR, though at a higher level (fig. 2b). Figure 3 shows the ratio between the calculated dose per kg BW for 0.045 and 0.050 mg/kg/day and the actual dose given in DTO (1.33 mg/m²/day). A dose of 0.045 mg/kg/day leads to 25% less GH in young girls, and a 20% higher dose in late adolescence. For 0.050 mg/kg/day, these figures are 15 and 30%, respectively. As expected, the effect of the dosing regimen is strongly influenced by the girls’ BMI SDS (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000357844).

Figure 2c shows the actual dose administered in S1–4, compared with the calculated dose based on BSA dosing. There were too few young girls to document the effect below 9 years. While the nominal BW-based dose at 10 years on the relatively low GH dose regimen of S1–4 is considerably lower than observed on a dose of 1.33 mg/m²/day in DTO, it is in the same range between 15 and 18 years (fig. 2a, c). Figure 2d shows the actual dose in S5 compared with the calculated dose per m² BSA. As mentioned earlier, above the age of 11 years the actual given dose was lower than the per protocol dose.

Adult Height Gain

Table 2 shows the AHG for the four cohorts. The lowest dose was used in S1–4 (0.033 mg/kg/day, approx. 0.92 mg/m²/day at a BSA of 1 m²), and a dose of 1.33 mg/m²/day was given in DTO and group A of DTDR. If only girls with spontaneous puberty were analyzed, the average effect of a higher dose appears to be 1.4 cm (7.4 cm on 1.33 mg/m²/day vs. 6.0 cm on 0.033 mg/kg/day). The dose given in group B of DTDR (with a calculated average dose of

Fig. 1. Mean ± SD IGF-I SDS against duration of treatment in clinical trials on GH treatment in TS. a DTO: data for all subjects grouped by Ox dose. Circle: GH 1.33 mg/m²/day + placebo (n = 46); square: GH 1.33 mg/m²/day + 0.03 mg/kg/day Ox (n = 44); triangle: GH 1.33 mg/m²/day + 0.06 mg/kg/day Ox (n = 39). b DTDR: data according to dose groups. Circle: group A (1.33 mg/m²/day, n = 20); square: group B (1.33–2.00 mg/m²/day, n = 21); triangle: group C (1.33 to 2.00 to 2.67 mg/m²/day, n = 21). c S1–4: data for all subjects (0.033 mg/kg/day), grouped by Ox dose. Circle: GH alone (n = 31); square: GH + Ox (0.05 mg/kg/day, n = 31).
0.0675 mg/kg/day) resulted in an AHG of 13.5 cm for all girls, compared to 11.2 cm on a similar per protocol dose (though the actual dose was 25% lower, 0.056 mg/kg/day) in S5 (p = 0.06). In girls starting before 8.00 years, AHG was 13.8 ± 2.8 (n = 15) versus 10.8 ± 4.2 cm (n = 6) (p = 0.06), while it was similar in girls 8–12 years of age (12.6 ± 5.3 vs. 11.6 ± 4.2 cm, p = 0.69). A graphical representation for patients without Ox cotreatment is shown in online supplementary figure 2.

**Cumulative Dose and Cost**

In DTO (n = 129) the mean ± SD actual cumulative dose was 3,695 ± 1,326 mg in comparison to 4,128 ± 1,354 mg on the hypothetical cumulative dose of 0.0475 mg/kg/day (p < 0.0001), assuming equal efficacy (fig. 4). The average financial saving if dosing by BSA in DTO would be approximately 10.5% (EUR 20,000) per patient. For group B of DTDR, the actual cumulative dose was 7,081 ± 1,668 mg, 14% lower than the hypothetical dose based on BW.
In S1–4 the actual cumulative dose was 2,591 ± 980 mg, 18% more than a hypothetical dose of 0.924 mg/m²/day (2,127 ± 739 mg). In S5 the calculated cumulative dose according to the protocol would have been 5,886 ± 1,460 mg, compared with a calculated dose per m² of 5,403 ± 1,241 mg. However, the dose actually given was lower (4,890 ± 1,499 mg) due to a 50% reduced GH dose in 4 of 13 girls and decreasing doses per kg BW over time.

**Discussion**

In this study, we investigated whether the theoretical arguments in favor of BSA-based GH dosing could be supported by empirical data by analyzing data of GH-treated girls with TS from two Dutch studies (using a BSA-based dosing regimen) and five Swedish studies (using a BW-based regimen). The results show that: (1) BSA-based dosing leads to stable serum IGF-I SDS levels over a period of
8–10 years, (2) BSA-based dosing leads to higher nominal doses in young girls (<9 years) and lower doses in adolescents than BW-based dosing, (3) AHG tends to be greater on a BSA-based regimen than on a BW-based regimen in patients who start GH treatment before 8 years of age, and (4) the cumulative dose and cost are lower on a BSA-based regimen. We therefore conclude that BSA-based dosing is more cost-effective than BW-based dosing.

The stable IGF-I SDS on all regimens suggests sufficient exposure to GH in childhood and adolescence, although this could only be studied in a narrow age range for BW-based dosing. The absence of the hypothesized increase in IGF-I SDS over time in girls treated with BW-based doses is probably due to the fact that IGF-I SDS has been described to significantly increase only after doubling of the GH dose [29].

The main difference between BSA-based and BW-based dosing is that the dose of the former regimen is relatively high in young patients and relatively low in adolescents. This confirms the results of a previous study on the
Table 2. AHG after GH treatment (without addition of Ox) in Dutch and Swedish TS studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose per protocol</th>
<th>Calculated average dose on alternative body size parameter</th>
<th>Duration of GH treatment, years</th>
<th>AHG, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTO</td>
<td>1.33 mg/m²/day</td>
<td>0.0475 mg/kg/day without Ox, divided per age group:</td>
<td>without Ox, divided per age group:</td>
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<tr>
<td></td>
<td></td>
<td>&lt;8: 9.3±2.0</td>
<td>&lt;8: 9.1±4.2 (n = 18)</td>
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<td></td>
<td></td>
<td>8–11: 5.1±1.3</td>
<td>8–11: 6.0±3.5 (n = 16)</td>
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<td></td>
<td></td>
<td>≥12: 3.4±0.8</td>
<td>≥12: 5.8±2.6 (n = 12)</td>
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<td></td>
<td></td>
<td>all: 6.2±3.0</td>
<td>for girls with spontaneous puberty</td>
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<td>(Pl and Ox): 6.7±2.9</td>
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<td>for girls with spontaneous puberty</td>
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<td></td>
<td>(Pl and Ox): 7.4±3.7 (n = 20)</td>
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<tr>
<td>DTDR (group B)</td>
<td>1.33 mg/m²/day during 1st year followed by 2 mg/m²/day</td>
<td>0.0675 mg/kg/day</td>
<td>all: 13.5±3.6 divided per age group:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>7.8±2.2</td>
<td>&lt;8: 13.8±2.8 (n = 15)</td>
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<td></td>
<td></td>
<td></td>
<td>8–11: 12.6±5.3 (n = 6)</td>
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<tr>
<td>S1–4</td>
<td>0.033 mg/kg/day</td>
<td>0.924 mg/m²/day</td>
<td>all: 4.9±1.9 (n = 79)</td>
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<td>without Ox, divided per age group:</td>
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<td>8–11: 4.8±5.3</td>
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<td>≥12: 4.5±4.6</td>
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<td>for girls with spontaneous puberty:</td>
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<td>4.6±2.7 (n = 25)</td>
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<td>for girls with spontaneous puberty:</td>
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<td>6.0±5.0 (n = 24)</td>
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<tr>
<td>S5</td>
<td>per protocol: 0.067 mg/kg/day</td>
<td>per protocol: 1.88 mg/m²/day</td>
<td>all: 7.1±2.0 (n = 13)</td>
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<tr>
<td></td>
<td>actual dose: 0.056 mg/kg/day</td>
<td>actual dose: 1.57 mg/m²/day</td>
<td>divided per age group: &lt;8: 8.9±1.3</td>
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<td></td>
<td></td>
<td></td>
<td>8–11: 5.6±0.7</td>
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<td></td>
<td></td>
<td></td>
<td>all (n = 13, of whom 8 with Ox): 11.2±4.0 divided per age group:</td>
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<td></td>
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<td></td>
<td>&lt;8: 10.8±4.2 (n = 6)</td>
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<td>8–12: 11.6±4.2 (n = 7)</td>
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</table>

Pl = Placebo.
KIGS database from the UK [32], showing that 5-year-old girls on BSA-based dosing received 33% more GH than those on BW-based dosing, similar doses at 10 years, and 10% lower doses at 15 years. In our analysis, the difference was less marked at a young age (15–25% more at 3 years) and more marked in adolescence (20–30% less at 17 years).

With respect to AHG, we acknowledge that caution is needed in comparing the results between the different studies. The growth response to GH in TS is dependent on many variables besides the GH dosage and mode of adjusting the dose for body size, such as the age at treatment initiation, parental height, duration of GH treatment, and start and dose of estrogens [25, 33]. We believe that the best way of dosing is to also take the individual responsiveness to GH into account, using prediction models for estimating the individual GH dose needed to reach a predefined height goal [34, 35]. In fact, this has been proven valid in a randomized clinical trial for children with GH deficiency and idiopathic short stature during a 2-year catch-up phase of growth [36], and should also be possible for girls with TS [33].

Since a young age at initiation of GH treatment correlates positively with AHG [37, 38], we grouped the patients into three age categories by their age at the start of GH treatment. However, a comparison between BSA- and BW-based dosing was still difficult for most study groups because the administered dosages were different. A direct comparison was only possible between the per protocol dose of 0.067 mg/kg/day in S5 (although the mean actual dose was 0.056 mg/kg/day) and the roughly equivalent dose of 2.0 mg/m²/day (after 1 year of 1.33 mg/m²/day) in DTDR. The results show that BSA-based dosing is particularly beneficial in girls who start GH treatment at an early age, suggesting that a somewhat higher dose at a young age has more influence on AHG than a relatively high dose in adolescence.

GH treatment for short stature in TS is very expensive. It has been estimated that approximately 97% of the costs of treating short stature in patients with TS are caused by GH, with mean costs of EUR 23,050–26,090 (equivalent to USD 30,000–34,000) per cm gained for TS patients for an average of 5 years of treatment [39]. The different scale of progression of BW and BSA implies that in adolescence, where BW has increased much more than BSA, BSA-based dosing leads to a significantly lower cumulative dose than BW-based dosing, and therefore to a lower total cost. We calculated that the average financial saving when dosing by BSA was in the order of EUR 20,000 per patient, and obviously more in overweight adolescents. Given the similar efficacy in terms of growth, at least in this dose range, our analysis suggests that dosing GH by BSA in girls with TS is more cost-effective than dosing by BW, particularly if treatment starts at a young age.

We assume that there are basically four reasons that in most countries the GH dose is calculated per BW. First, it is easier since for BSA an additional arithmetical step is needed to calculate BSA from height and weight. Second, some physicians may doubt which formula one should use to calculate BSA [40], although we believe that the formula proposed by Mosteller [22] \[\text{BSA (m}^2\) = √ \text{weight (kg) × height (cm)/3,600}\] is easy to use and is well validated. Third, in most reports on GH treatment, as well as in prediction models [25], dose is given per kg BW. Fourth, one may hypothesize that dosing per BW may have a concomitant advantage in adolescence in mimicking the increased GH secretion during puberty (which, however, is fourfold in normal girls) [41] and because the dose-response relation between GH secretion and growth rate is logarithmic. Still, we believe that the appropriate catch-up growth and better cost-effectiveness of BSA-based dosing, and the prevention of high doses in obese girls with BW-based dosing, argue in favor of a BSA-based regimen. However, it is conceivable that if a relatively low BSA-based dose is administered to GH-deficient patients, like in Australia and New Zealand, the nominal dose may get too low, as suggested in a recent report [3].

There are some limitations to this study. First, this was a retrospective analysis using data that were not designed to answer the question of whether dosing based on BSA is better than dosing based on BW. Further, GH doses and brands were different across studies, and concomitant estrogen and Ox treatment differed. Other factors, including level of compliance to the study regimen, may also have contributed to differences between studies.

In conclusion, we have shown that the theoretical arguments in favor of BSA-dosing GH in girls with TS are supported by a stable serum IGF-I SDS during GH treatment, good efficacy, and better cost-effectiveness, especially if GH dosing starts at a young age, in comparison to BW-based dosing.

**Acknowledgements**

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Disclosure Statement

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GH Dosing in TS Girls


